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MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND
FOREIGN AUTHORS

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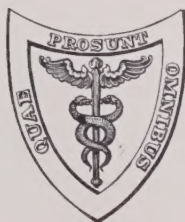
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VOLUME II

DISEASES CAUSED BY PROTOZOA AND ANIMAL PARASITES—
DISEASES DUE TO PHYSICAL, CHEMICAL, AND ORGANIC
AGENTS—DISEASES OF METABOLISM AND OF
THE RESPIRATORY SYSTEM

SECOND EDITION, THOROUGHLY REVISED

ILLUSTRATED



EUGENE F. McCAMPBELL

LEA & FEBIGER
PHILADELPHIA AND NEW YORK
1914

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PART I

PROTOZOAN INFECTIONS

CHAPTER I

AMŒBIC DYSENTERY

By RICHARD P. STRONG, M.D.

Synonyms.—Amœbic Colitis; Amœbic Enteritis; Entamœbiasis.

Definition.—An infectious disease characterized by a variable mode of onset, a course of great irregularity, intestinal disturbances consisting chiefly of intermittent attacks of diarrhœa and constipation, abdominal pain, and the presence of amœbæ, and frequently of mucus and blood in the dejecta. Besides man, in the tropics smaller monkeys and orang-outangs are attacked.

Etiology. Distribution and General Prevalence.—The disease is widely prevalent and occurs sporadically in most subtropical and temperate countries, but in tropical ones it finds its endemic home and is the usual form of dysentery. It is particularly prevalent in the Philippine Islands, India, and Egypt, and it is common in South America, particularly in Brazil, and in the Southern United States; sporadic cases are found from time to time in New England, and an occasional case is encountered in the Eastern, Central, and Western States. In the eastern hemisphere cases have occurred in most of the countries of Europe and in parts of Asia and Australia. Cases have been reported in individuals who have never lived outside of Great Britain or France. In temperate climates the disease is rarely epidemic, but occasional outbreaks of moderate size have occurred.

In 1899-1900 an epidemic of bacillary dysentery occurred in the Philippine Islands, and in a series of 147 fatal cases of this and of the amœbic form, 67 per cent. belonged to the latter variety. Of the dysentery cases encountered by the writer in Manila during fourteen years, fully 60 per cent. have been amœbic, and the great majority of the fatal cases of dysentery in adults showed lesions of this form at necropsy. The disease is the most prevalent one in the Philippine Islands among white people. However, during the past few years, the percentage of amœbic dysentery among white patients has steadily decreased in the Philippine Islands, largely owing to greater hygienic precautions. Deeks¹ points out that in the Panama Canal Zone there has been a marked decrease in the number of amœbic dysentery cases in the past

¹ *Jour. Am. Med. Assn.*, 1913, lx, 40.

few years. Rogers¹ has shown that in India the amœbic form of dysentery is by far the most prevalent type and that more deaths occur from this form.

Meteorological conditions have considerable influence upon the prevalence of the disease. In the Philippine Islands by far the greatest number of cases is recognized between June and September, the largest number appearing after the heavy rains have begun. Harris states that the onset of the malady in the United States is almost invariably in the summer months, May, June, July, and August. Greig and Wells² found that in Bombay, during the years from 1909 to 1911, amœbic infection showed a marked seasonal variation closely associated with variations in humidity, but not corresponding with those of temperature, and reaching a maximum in August.

Sex.—All observers agree that the disease is much more prevalent in males. Harris states that it seems to occur in males about three times as frequently as in females. In Fitcher's series of 119 cases at the Johns Hopkins Hospital, there were 108 males and 11 females. In the Philippine Islands the disease occurs also more frequently in males. In the Government Civil Hospital of 401 cases, the ratio of males to females was as 4.1 to 1. In 200 personal cases which were analyzed for statistical purposes only 23 have been in females.

Age.—In Fitcher's series the greatest number of cases occurred between the ages of twenty-one and thirty years. Of the writer's, 149 among 200 were in the third and fourth decade; only 4 cases occurred in the second. The disease is common in children under ten years of age. Fitcher called attention to 11 such cases. Musgrave has encountered 21 with 1 death in a series of 100, and the writer met with 18. Harris reports 4 cases out of 35, and many other observers have encountered the disease in young children.

Race.—In the Philippine Islands the white race is much more susceptible than the Malay. The natives, by reason of their mode of life and condition of their drinking water, are very frequently exposed to infection, yet they do not suffer so often or usually as severely from it as Americans and Europeans. Fitcher and Harris found that in the United States blacks were less frequently attacked than whites.

Unhygienic Influences.—It has been stated that amœbic dysentery is an affection preëminently of the poor, and is almost always associated with filth, bad hygienic surroundings, and lack of proper food. This does not hold good in the tropics, and for example, in the Philippine Islands, or in India all classes are likely to be attacked who do not take proper precautions in regard to their drinking water. Susceptibility seems to depend considerably in some cases upon the general physical condition, although sometimes apparently perfectly healthy and robust persons are attacked.

The Amœbæ of the Human Intestine.—These organisms are classed under the rhizopoda of the protozoa. They are unicellular parasites

¹ *Lancet*, 1912, ii, 1062.

² *Scientific Memoirs of Medical Officers, India*, 1911, No. 47

possessing an endosarc and ectosarc which can readily be distinguished when the organism is in motion. The endosarc is granular, and usually encloses several vacuoles of variable size. The ectosarc is clear and more hyaline in appearance. When seen in the feces they frequently contain red blood corpuscles, the larger forms sometimes enclosing as many as twenty. Pigment granules and bacteria have also been observed in the endosarc. The parasite moves by means of pseudopodia; blunt processes consisting of the ectosarc are first protruded and into these protrusions the protoplasm of the endosarc appears to flow. It possesses a nucleus which may sometimes be observed in the living forms but which can be more clearly seen in colored preparations. For bringing out the structure of the parasite in smear preparations made from the stools or from cultures, iron hematoxylin, Delafield's hematoxylin, and borax carmine are all satisfactory. The preparations should be fixed while moist. For staining the amœbæ in sections after proper fixation, Giemsa's stain, as modified by Wolbach,¹ is recommended.

The diameter of the organisms found in the human stools has been variously estimated at from 10 to 50 μ . Prowazek² has recently described a new human species *Entamoeba hartmanni*, in which the size varies between 4 to 13 μ . The size may vary considerably according to the stage of the life cycle observed. Refractile homogeneous cysts of the amœbæ may also be found in the stools under certain conditions. Reproduction is affected either by binary or by multiple fission.

Biological Properties.—It is doubtful if amœbæ have been grown artificially in pure culture free from bacteria, though numerous attempts have been made to accomplish this since the reported successful results of Kartulis in 1885. He used a straw decoction as a medium, and thought that he had obtained a pure growth of the parasites from an abscess of the liver which was free from bacteria. In 1895, C'elli and Fioeca and Cassagrandi and Barbagallo claimed to have obtained, after great difficulty, amœbæ in pure cultures upon an alkaline media containing fucus crispus. However, the organism did not reproduce in transplants. Williams³ has reported the cultivation free from bacteria of amœbæ found in the intestine of mammals, upon crushed brain, liver, kidney, and other tissues of the rabbit or guinea-pig streaked on nutrient agar. While other observers have not been successful in cultivating amœbæ free from bacteria, single species have been grown with pure cultures of bacteria by many workers. The free living amœbæ may be easily grown upon a great variety of media providing the substance used does not offer conditions so favorable for the growth of bacteria that they will overgrow the protozoa. Dilute peptone solution constitutes a very favorable fluid medium. Beyernick recommended agar which has been repeatedly abstracted with water after sterilization. Frösch⁴ obtained the best results upon a medium composed of agar, 0.5 gram; ordinary

¹ *Journal of Medical Research*, 1912, xxvii, 83.

² *Archiv für Protistenkunde*, 1912, xxvi, 243.

³ *Journal of Medical Research*, 1911, xxv, 263, and Collected Studies of Research Laboratory, Department of Health, New York City, 1911, vi, 298.

⁴ *Centralbl. für Bakt.*, Part 1, xxi, 1897, 926.

alkaline bouillon, 10 grams, and tap water, 90 cc. Musgrave and Clegg recommended agar-agar 20 grams, sodium chloride and extract of beef each 0.3 to 0.5 gram, prepared as ordinary bacterial agar and with a final reaction of 1 per cent. alkaline to phenolphthalein. From more recent experimental work, it would appear that all the species of amœbæ which have been cultivated upon artificial media are free-living amœbæ and that the true parasitic species are obligatory parasites and are incapable of multiplication outside their host.

Behavior toward Physical Conditions and Chemical Substances.—The amœbæ of the intestine are usually destroyed by a temperature of 60° C. maintained for one hour even when encystment has occurred. They usually lose their motility in the stools at low temperatures and quickly die, but when encystment has occurred, freezing for as long a period as a month may not destroy them. The action of various *chemical substances* has received attention for a long time. Harris found that amœbæ (in the stools) were not seemingly affected by saturated solutions of quinine sulphate or boric acid, though 1 to 300 solution of quinine bisulphate invariably killed them within ten minutes. They were destroyed by weak solutions of hydrogen dioxide, potassium permanganate, toluidine blue, and dilute acids. Rogers found in scrapings from the walls of amœbic liver abscesses that a solution of quinine, 1 to 1000, failed to kill the parasite even after several hours. On the other hand, 1 to 500 solution stopped all movement of the amœbæ in from five to fifteen minutes. In order to test if such a strength would be effective when applied to the living wall of an abscess, a piece of such tissue which was full of active amœbæ was placed in a solution of 1 to 500 sulphate of quinine in normal salt solution, and scrapings examined every five minutes. In none of them were any living parasites found.

Tuttle found that 1 to 10,000 bichloride of mercury and 1 to 100 nitrate of silver solutions check the motility but do not destroy the parasite except after prolonged contact. Saline solutions and 5 per cent. of the 15-volume peroxide of hydrogen in water also did not seem to destroy the amœbæ at body temperature. However, in the hands of this observer all of these substances when used at a temperature below 70° F. proved fatal to the motility and life of the parasite.

Musgrave and Clegg found that when a slant culture of amœbæ with bacteria was treated with a 1 to 2500 solution of quinine hydrochlorate, the parasites quickly encysted and in from five to eight minutes many had broken up and disappeared. Ten minutes later cultures were made but no development of amœbæ occurred in the fresh inoculations, although the bacteria grew out well. In an experiment with another amœba, a slight growth was observed. Acetozone, 1 per cent. acid to phenolphthalein, in solutions of 1 to 5000 and 1 to 2000, always killed amœbæ in cultures. Thomas found that in cultures of amœbæ in symbiosis with cholera spirilla, thymol, 1 to 2500, applied for fifteen minutes, had the most marked effect, in some instances destroying the amœbæ, while exercising only a moderate effect on the cholera spirilla.

In the summer of 1910 Bowman and the author studied in a comparative way the effects of suspensions of ipecac, solutions of emetine and

PLATE I



Colon in Amoebic Dysentery.

PLATE II



Colon in Amœbic Dysentery.

PLATE III



Colon in Amoebic Dysentery.

solutions of quinine sulphate upon different cultures, containing either motile or encysted forms of a free living species of amœbæ isolated from human stools and upon motile amœbæ in the stools of dysenteric cases. The experiments were carefully controlled. A suspension of ipecac, 1 to 25 in distilled water, destroyed all the motile amœbæ in cultures within twenty-four hours and subsequently amœbæ did not develop from the cysts treated in this way. In the parallel cultures treated with quinine sulphate solution 1 to 1000, all of the motile amœbæ were destroyed, but in one of the three experiments amœbæ developed from the cysts which had been in contact with the solution. In the control cultures motile amœbæ were abundant. In a second series of experiments with an ipecac suspension of 1 to 1000 and quinine sulphate solution 1 to 1000, the ipecac suspension failed to kill the motile amœbæ in all of the tests, while the quinine sulphate solution did so. However, in all the experiments of this series, amœbæ developed from the cysts which had been in contact with these substances. In a third series in which the cultures were tested with ipecac suspension 1 to 500, and quinine sulphate solution 1 to 1000, the ipecac suspension destroyed all the motile amœbæ in one of the tests but failed to do so in two other instances. Amœbæ developed from the cysts so treated in all three of the experiments. The quinine solution destroyed the motile amœbæ in all three of the experiments, but in one of these tests amœbæ developed from the cysts which has been in contact with the quinine solution. In a fourth series, with a solution of emetine, 1 to 50, all the motile amœbæ were destroyed and no amœbæ developed later from the cysts which had been in contact with the emetine solution. Dioxychinolin sulphate in a solution of 1 to 100 or 1 to 1000 apparently also destroyed both the motile amœbæ and prevented the subsequent development from the cysts. Chinosol was found to be inferior to quinine sulphate in its action.

According to Vedder¹ the fluid extract of ipecac will destroy amœbæ in cultures in a solution of 1 to 10,000, or in some instances 1 to 100,000, while he found that de-emetized ipecac was practically inert against the amœbæ. Wherry² found that emetine 1 to 20,000 dilution killed the motile forms in cultures in only one of five series of experiments after 23.5 hours exposure at 36–38° C. None of the amœbæ were killed after one hour exposure. Lyons³ found that on cultures of amœbæ ipecac apparently possessed but slight inhibitive power on the amœbæ. Salicylic acid, however, revealed a marked destructive action upon amœbæ in dilutions up to 1 to 500. Rogers⁴ claims that entamœba histolytica in stools is immediately killed by 1 to 10,000 solution of emetine hydrochloride and that solutions of 1 to 100,000 rendered the amœbæ inactive and apparently killed them.

In regard to special *physiological processes* of dysenteric amœbæ, little is known. We are aware that certain definite secretions occur in the

¹ *Transactions Far Eastern Association of Tropical Medicine*, Hong Kong, 1912, 87; also *Bulletin Manila Medical Society*, March 1911.

² *Journal Infectious Diseases*, Chicago, 1912, x, 162.

³ *New Orleans Medical and Surgical Journal*, 1912, lxiv, 881.

⁴ *British Medical Journal*, 1912, i, 1424, and ii, 405.

protoplasmic body, some of which evidently go to make up the mantle which forms about the parasite in encystation. It has been supposed that the engulfing of certain substances in the protoplasm—red blood corpuscles, bacteria, granular material, etc.—occurred for the purpose of nourishment. Some have thought that the pigment masses which amœbæ sometimes contain are the remnants of partially digested red cells. Mouton obtained a proteolytic ferment, resembling trypsin, from cultures of free living amœba isolated from garden earth, and grown in symbiosis with the colon bacillus.

Distribution of Amœbæ in the Body.—Besides the intestine and neighboring tissues, and abdominal cavity, abscess of the liver, lung, pleura, and brain, amœbæ have been found in the following pathological conditions: in ascitic fluid in cases of abdominal tumor; in necrosis of the jaw bone; in abscess of the mouth; in the pelvis and tubules of the kidney, in subcutaneous tissues and in perineal sinuses, and in the bladder and urine. Musgrave reported their presence in the circulating blood in two cases. Celli and Fiocca reported their cultivation from the larynx and lungs in cases of tuberculosis, and Gross and Sternberg and Prowazek found them in tartar scraped from the teeth. These amœbæ are obviously not all of the same species. Frequently when present in the bladder a sinus leading into the rectum is found, or one has previously existed, but this is not always the case.

Classification.—A great many species of amœbæ are found living within the bodies of animals of all kinds, chiefly within the digestive tract, and frequently give rise to no disturbance. Therefore it is essential to have some knowledge of the classification of these organisms. Lösch in 1875 gave the name *Amœba coli* to the species which he found in the human intestine, and thus this organism came to be placed in the genus *Amœba* Ehrenberg. In 1879 Leidy established the genus of *Entamœba* for the parasitic species found in the common cockroach and named it *Entamœba blatta*. In 1897 Cassagrandi and Barbagallo, after a study of human intestinal amœbæ, established the genus of *Entamœba* for these organisms and named the species they encountered *Entamœba hominis*. Quincke and Roos, Kruse and Pasquale, Celli and Fiocca, and the writer all recognized from morphological differences, from clinical observations, and especially from experiments upon animals, that more than one species of entozoic amœba occurred in man, and these species were described under a variety of names. From a zoölogical standpoint the evidence of the plurality of species was not entirely complete.

Schaudinn,¹ however, in 1903 greatly advanced our knowledge by distinguishing two distinct species of amœbæ which he described in detail. One of these species, which occurs commonly as a harmless inhabitant of the intestine and not as a parasite, he named *Entamœba coli*, and the second species, a parasitic one, he designated as *Entamœba histolytica*. This second species was regarded as the cause of amœbic dysentery and amœbic liver abscess. In adopting the terminology of *Entamœba coli* and *Entamœba histolytica* for the human entozoa, Schaudinn maintained

¹ *Arbeiten aus dem Kaiserlichen Gesundheitsamte*, 1903, xix, 547,

that the description of Lösch was incomplete and that the genus *Entamæba* established by Cassagrandi and Barbagallo according to the law of priority must be accepted. However, as the species *Entamæba hominis* was probably identical with that one of Lösch (*Amæba coli*) that species should be correctly designated as *Entamæba coli*.

The two species *Entamæba coli* and *Entamæba histolytica* can be distinguished by structural characters. *Entamæba coli* has a relatively fluid body, the ectoplasm is feebly developed and is not well differentiated, being usually only visible in the formation of pseudopodia. It has a large spherical nucleus, sometimes multiple, situated in the endoplasm. *Entamæba histolytica*, on the other hand, has a plainly developed ectoplasm, more strongly refractive and more hyaline in appearance than in *Entamæba coli*. The nucleus is smaller than in *Entamæba coli* and is difficult to recognize in fresh unstained specimens. It often has a compressed form, stains feebly, and is situated eccentrically in the endoplasm or immediately below the ectoplasmic layer. The life cycle of the two species is also different. According to Schaudinn, in the amœboid multiplicative stage *Entamæba coli* reproduces itself by binary fission and also by a process of multiple fission in which the nucleus divides until there are eight nuclei in the body; the characteristic eight nucleate amœba then divide into eight small amœbæ, each of which grows to an adult form, and the size of the organism consequently varies considerably. The propogative stage begins with the formation of a gelatinous envelope about a full-sized amœba with a single nucleus. The nucleus first divides into two and then undergoes a complicated series of changes including an autogamy of the reduced nuclei. When it is complete a tough, resistant cyst is formed within the soft gelatinous appearing envelope and each of the resulting nuclei or synkarya divides twice to produce four nuclei. In this way eight nucleate cysts are formed.

According to Schaudinn *Entamæba histolytica* produces itself by binary fission and by a process of budding (gemmation) in which the nucleus multiplies by division and then small amœbæ, each with a single nucleus, become budded off from the surface of the body. In the propogative stage of *Entamæba histolytica*, a cyst is not formed around the whole body but the nucleus becomes resolved into particles which contain chromidia. These spores then collect near the surface and later form buds. Around each of these buds a hard impervious membrane is formed within which no further development can be observed. These sporocysts then separate from the body of the organism, which dies off, and they constitute the resistant stage which serves for the transmission of this species to a new host. Subsequent investigation has thrown doubt upon the life cycle of this species as described by Schaudinn,¹ but his work has been followed by extensive studies relating to the human entozoa; more than a dozen other species have been described by various investigators.² A number of these species are founded upon insufficient

¹ Hartmann, *Handbuch der Pathogenen Protozoen*; Prowazek, Leipzig, 1912, i, 50; also *Archiv für Protistenkunde*, 1911-12, xxiv.

² For a summary of these species see Fantham, *Annals Tropical Medicine and Parasitology*, 1911, v, 111; and Prowazek, *Archiv für Protistenkunde*, 1912, v, 273 and xxvi, 241; also Walker, *Philippine Journal of Science*, 1911, vi, 260.

data and it is probable that later, some at least, will be found to be identical with those previously described.

While it is still doubtful how many distinct species occur in man most observers recognize at least two and several authorities three, namely, *Entamæba coli*, *Entamæba tetragena*, and *Entamæba histolytica*. In 1907 Viereck¹ described a species of amœba occurring in two cases of dysentery in India which he named *Entamæba tetragena*. This same species was shortly afterward described by Hartmann in eleven cases of dysentery from Africa. It has been found since to have a wide geographical distribution both in tropical and temperate climates, and has been reported particularly in cases of dysentery originating in Africa, India, Indo-China, China, Sumatra, Java, the Philippine Islands, Brazil, Panama, the eastern and western United States, and certain countries in Europe. It undoubtedly appears to be the usual species encountered in cases of human amœbic dysentery. Some authorities regard it as identical with *Entamæba histolytica*, and consider the description of the life cycle of *Entamæba histolytica* given by Schaudinn to be incorrect in some respects, and that either he did not observe the entire life cycle or that he confused stages of different species in the same life cycle. Thus Hartmann has found in an examination of Schaudinn's preparations and his own that most of them are *Entamæba tetragena*, and that the life cycle is considerably different from that previously described for *Entamæba histolytica* and that a process of autogamy does not occur. Walker believes that tetragena is probably only a variety of histolytica.

Entamæba tetragena has distinct refrangent ectoplasm, vacuolated entoplasm, and active motility, but the nucleus is large and distinct, is rich in chromatin and possesses a distinct nuclear membrane. Chromidia occur in the cytoplasm. Multiplication occurs by binary fission; sexual reproduction takes place by endogenous encystment which is preceded by nuclear division into two, reduction and then autogamy. The sporocysts develop only four nuclei instead of eight as in *Entamæba coli*.

In addition to these species of amœbæ, a number of free-living non-parasitic species have been cultivated on artificial media from human feces, which have either been ingested and passed through the digestive tract in this encysted condition, or which have been deposited in the stools after they have been passed and have emerged from their cysts in the cultures. Thus Wells² found that in India amœbæ of at least two types were commonly present in the air and that these could readily gain access to specimens of feces even though these were carefully collected. These amœbæ for the most part are of the limax type and while they have been frequently confused with the human entamœbæ, they at least usually can be distinguished from these by certain differences in the life cycle, such as the type of autogamy, or by the presence of a contractile vacuole.³ Thus Craig⁴ under the name of *Amœba lobospinosa*

¹ *Archives für Schiffs und Tropen Hygiene*, 1907, xi, Bieheft 1.

² *Parasitology*, 1911, iv, 204.

³ See Hartmann, Werner, Whitmore (*Archiv für Protistenkunde*, 1911, xxiii); Walker, loc. cit.; Craig, *American Journal of Medical Sciences*, 1913, cxlv, 83.

⁴ *Journal of Medical Research*, 1912, xxi, 1.

has described in detail a species of amœba grown in artificial culture media which possesses a contractile vacuole, cysts with one nucleus and the presence of lobose and spinose pseudopodia—characteristics which serve to distinguish it from the parasitic amœbæ occurring in man. This species was formerly supposed to be pathogenic for monkeys and man.

Occurrence of Amœbæ in Healthy Persons.—The presence of amœbæ in the stools of apparently healthy individuals formerly inclined many authors to believe that all amœbæ were without etiological or pathological significance. Schuberg, in 1893, found amœbæ in the stools of 10 out of 20 healthy persons to whom a dose of Carlsbad salts had been given. Kruse and Pasquale, in 1894, when perfectly healthy, observed amœbæ in their own feces and in those of 38 persons either healthy or suffering with diseases other than dysentery. Upon some of these, fresh autopsies were performed and the intestine carefully examined. In 1899 Musgrave and the writer found that 4 per cent. of patients examined in the Philippines who had no dysentery or history of the disease harbored amœbæ. A dose of Rochelle salts had been given to these individuals by the mouth previously. Schaudinn found amœbæ which he considered harmless in the stools of 34 of 68 healthy people in East Prussia, in one-fifth of the cases examined in Berlin, and in 256 out of 385 in Austria. The amœbæ found in the human intestine which do not give rise to disease are usually of the *Entamoeba coli* type, which has been found to have a wide geographical distribution. Schaudinn twice infected himself with this amœba and controlled his feces before infection for two months, in order to be sure that his stools were free from this organism. After infection he suffered from no intestinal disturbance. In Manila as high as 70 per cent. of the healthy American soldiers were found by Ashburn and Craig to harbor *Entamoeba coli*. From its frequent occurrence in healthy individuals for very long periods of time without symptoms of diarrhœa and dysentery, and from the negative results obtained from it in animal experiments, it has generally come to be regarded as a harmless commensal of man. For further details regarding this species the reader is referred to the recent article of Werner.¹

On the other hand, there are periods in the course of amœbic dysentery, particularly in the earlier stages, in which symptoms are entirely lacking. Hence when amœbæ of the *Entamoeba tetragena* or *histolytica* type are found in the stools of healthy individuals we cannot say that they are not suffering with an early or latent form of the disease, or that the malady does not exist in its incubation period, unless we follow them over long periods of time in which no disease develops. In other cases in which infection with the *Entamoeba tetragena* or *histolytica* type is present, the infection may be of so mild a character as to produce practically no symptoms unless the resistance of the patient is lowered by other intercurrent disease. It is not necessary to suppose in these cases that lesions of the intestine are always present, although in some lesions may exist which we cannot always be aware of during life. A few observers incline to the belief that all amœbæ are pathogenic and maintain that in every

¹ *Handbuch Pathogen. Protoz.*; Prowazek, Leipzig, 1912, i, 67.

case where human infection is found, even though there be no symptoms, local treatment should be insisted upon until the amœbæ disappear. We know nothing yet as to whether the pathogenesis of some species of amœbæ under certain conditions may be increased by long periods of existence in the human intestine.

Occurrence of Amœbæ in the Stools of Those Suffering with Other Diseases than Dysentery.—Another argument advanced against the etiological significance of amœbæ in dysentery, is the fact that these organisms have been found in the intestines of those suffering with other diseases, such as chronic diarrhœa, cholera, typhoid fever, etc. In many of the reported cases the chronic diarrhœa might be regarded as a symptom of pathogenic amœbic infection. But in some of these the *Entamoeba coli* may have been the form of protozoön present. Kruse and Pasquale found no lesion at autopsy in some of their patients in whom amœbæ were present.

In the tropics, where amœbic dysentery is so common and frequently of long standing, concomitant occurrence with typhoid fever, cholera, or tuberculosis, is not so very uncommon. In the writer's series of 100 fatal cases of amœbic dysentery in soldiers there were 4 cases of concomitant infection with typhoid fever, in 1 of which death occurred from a perforation in the ileum.

The Non-occurrence of Amœbæ in the Stools of Dysenteric Patients.—Many observers have advanced the argument that since amœbæ are not found in the feces or in the intestines of those suffering with tropical, epidemic, or sporadic dysentery, these organisms are not the cause of the disease. Shiga in Japan, Flexner and the writer in the Philippines, and Leonard Rogers in India, have shown that tropical dysentery consists of at least two forms, one due to a species of amœbæ and the other to a species of bacterium. These conclusions have been confirmed also for temperate climates. In addition to these forms there is a third, catarrhal dysentery, which is seen occasionally in the tropics, and has a variable etiology. It is occasionally indistinguishable clinically from amœbic dysentery.

Inoculation Experiments.—Several methods have been chiefly employed. (1) The direct injection into the rectum of feces containing the parasites. In this manner positive results have been obtained in cats and dogs. In these experiments not all the inoculated animals became infected, and single experiments and those in which unsuitable material is employed are likely to fail. However, there is no doubt that lesions may be produced in the large intestine in cats by this method. (2) By feeding encysted forms of amœbæ. Cassagrandi and Barbagallo, Calandruccio, and Schaudinn fed themselves encysted amœbæ, apparently of the *Entamoeba coli* type, produced infection, and reobtained the amœbæ from their stools. They had no symptoms of disease following the infection. They also infected cats by feeding encysted cultures of this parasite but obtained no symptoms of disease. Upon feeding the cysts of *Entamoeba histolytica* to cats, Schaudinn obtained dysentery and ulceration of the large intestine in which numerous amœbæ were found. Quincke and Roos fed stools containing encysted amœbæ to two cats and obtained infection and amœbic ulceration, which they observed at

autopsy. Musgrave fed encysted amœbæ in cultures with bacteria to monkeys and obtained, in a small percentage of the cases, dysentery and ulcerations in which amœbæ were found.

Other observers have claimed that natural infection in the monkeys employed in these experiments was not carefully excluded. Both the lower monkeys and orang-outangs contract the disease naturally and at one time as many as four or five of our laboratory animals were found to be suffering with naturally acquired infection. Greig and Wells¹ have recently shown that in India natural infection in monkeys is very common; of the 53 monkeys examined all showed amœbæ in the feces which appeared and reappeared at irregular intervals so that repeated examination was sometimes necessary to discover them. Some of these animals seemed perfectly healthy while others had dysenteric symptoms. Franchini² has recently shown that in a healthy monkey amœbic dysentery and typical lesions may be produced by rectal injections of *Entamœba tetragena*. Castellani³ observed in a monkey the occurrence of amœbæ in an abscess of the liver in which no bacteria could be discovered. There were no evidences of disease in the intestine. The abscess was not produced by inoculation but occurred spontaneously. Werner, Darling, Fanthan and others have produced dysentery in kittens by feeding the feces containing the cysts of either *Entamœba histolytica* or *tetragena*, while feeding the cysts of *Entamœba coli* to kittens has produced infection in some instances but no symptoms of dysentery. Wenyon⁴ not only produced dysentery in kittens by inoculation of the feces, but in one instance amœbic abscess of the liver, which developed spontaneously, apparently as a result of the amœbic intestinal infection.

Against the experiments, in which bacteria together with the amœbæ were employed, being used as an argument in favor of the pathogenesis of the parasites, objection was naturally urged. Therefore attempts were made to employ material in which amœbæ were present without microorganisms. Kartulis and Kruse and Pasquale used the contents of liver abscesses free from bacteria and produced dysentery and ulcerations in the intestines of cats by rectal injections. They stated that while the lesions in their most successful experiments bore in many points a striking resemblance to those seen in man, they were not identical. In 1899 the writer obtained dysentery and perfectly typical amœbic ulcerations in the large intestine of cats by the injection into the rectum of portions of the contents of a liver abscess which contained living amœbæ but was otherwise sterile. These lesions were *perfectly typical of the lesions seen in man*. Many of the ulcers showed a distinct undermining of the mucosa and a round-celled infiltration of the submucosa, with numerous amœbæ at the base of the ulcers. Some of these specimens are now in the Army Medical Museum in Washington. These experiments were practically conclusive of the pathogenesis of this species of amœba. It is possible that toxic substances may be introduced with

¹ *Memoirs Sanitary Department of the Government of India*, 1911, N. S., 47.

² *Centralbl. für Bakt.*, Jena, 1911-12, Part 9, xli, 590.

³ *Parasitology*, 1908, i, 101.

⁴ *Journal London School Tropical Medicine*, December 1912, ii, Part 1.

the amœbæ in the pus of these liver abscesses, and it might be argued that these cause erosions of the mucosa. However, a chemical substance alone could hardly produce the typical anatomical lesions of the disease which are so peculiar to amœbic infection alone and which no one has produced without amœbæ. Very recently Walker has performed feeding experiments upon man with the cysts of *Entamœba coli* and *histolytica* or *tetragena*. His results bear out those which have been obtained on animals, namely, that successful infestation of man with *Entamœba coli* does not give rise to intestinal disturbance, while infections with *Entamœba histolytica* produces dysentery.

Source of Amœbæ and Mode of Infection.—The greatest source of infection is through drinking water contaminated directly or indirectly with fecal material from cases of amœbic dysentery. Food, particularly when uncooked, such as salads, lettuce, etc., may also be a source of infection. The amœbæ which are found almost constantly in the water in certain tropical countries and which have been easily cultivated on artificial media, as Walker has shown, are usually of the limax type and belong to the genus *Amœba* Ehrenberg. They possess a contractile vacuole and other points in morphology and in their life history which serve to distinguish them from the parasitic species. It is the consensus of opinion at the present time that they are not capable of producing disease in man. It is known, however, that infection with *Entamœba* of the *histolytica* or *tetragena* type may persist in many instances for long periods of time after the symptoms have subsided, during which time the encysted entamœba may be passed in the stools and constitute an important source of infection to other individuals provided they come into contact with their food or drink. In tropical countries open reservoirs and tanks containing drinking water may perhaps be polluted by the excreta of infected monkeys. It is true that all those who harbor the pathogenic form do not suffer with the disease amœbic dysentery. Dilute acids quickly kill amœbæ and it is probable that many of those ingested are destroyed in the stomach. Natural and, in the natives, acquired immunity from constant exposure to the disease may also exist, and probably in these cases the disease results only when the system is overwhelmed with very large numbers of the parasites or when it is weakened by other disease.

Other Organisms in Amœbic Dysentery.—Other protozoal organisms common in the intestine in amœbic dysentery are the trichomonas, *Cercomonas intestinalis*, and *Megastoma entericum*. These, when present in very large numbers, probably by their rapid mechanical movements, act as an irritant to the already inflamed mucosa. Other animal parasites which are found not infrequently in the intestine of those who suffer with amœbic dysentery in the tropics are the *Tænia saginata*, *Ascaris lumbricoides*, the *Tricocephalus trichuris*, *Uncinaria duodenale*, *Strongyloides intestinalis*, and *Oxyuris vermicularis*; *Balan-tidium coli* may likewise be present and give rise to intestinal lesions. In Egypt the ova of *Bilharzia hæmatobia* may in addition be found in the stools. When these parasites are present the cases may be regarded as those of multiple infection. Schaudinn stated that certain species of

bacteria found in dysentery apparently exert a distinctly harmful influence upon *Entamæba coli* and monads which may be present in the intestine at the same time. This is not true of *Bacillus dysenteriae* and the dysenteric amœba, since in some cases both of these parasites produce lesions side by side in the large intestine.

Bacteriology.—Kruse and Pasquale investigated the organisms found in 14 cases of the disease and isolated streptococci, *Staphylococcus pyogenes*, typhoid-like bacilli, *Bacillus pyocyaneus*, and *Bacillus claratus*. None of these was present so constantly or in such numbers as to suggest a specific relation to the disease. Of 6 cases in which pure cultures of *Bacillus pyocyaneus*, *Bacillus claratus*, the streptococcus, or typhoid-like bacilli, were introduced into the rectum of cats, in 5 the results were negative; in the sixth, in which the streptococcus was employed, there was no dysentery, but a catarrh of the intestinal tract and septicæmia.

In 26 of my fatal cases, in plate cultures from the large intestine several varieties of the colon bacillus were the only organisms found constantly present. We were unable to produce dysentery or any lesions in cats by rectal injection of cultures of the varieties of the colon bacillus encountered. In 76 fatal cases cultures were made from the solid organs. The bacteria encountered were streptococci and staphylococci, *Diplococcus pneumoniae*, colon bacilli, the typhoid bacillus, and *Bacillus aerogenes capsulatus*. The most striking fact demonstrated by these examinations was that 5 per cent. of the cases succumbed from a general terminal infection with the *Staphylococcus* and *Streptococcus pyogenes*.

Pathology.—The Large Intestine.—The large intestine is chiefly involved. The most striking feature in chronic cases is the great thickening of its walls. This may be confined to the submucosa or involve all the coats. It is always more marked in the submucosa and is due to a general œdema and localized areas of thickening. The other characteristic lesions consist chiefly of hemorrhagic catarrh, of raised hemispherical areas of infiltration protruding above the level of the surrounding mucosa, and of at least three forms of ulceration. Frequently a diphtheritic process is added to the amœbic one. The lesions may affect the whole large intestine or a portion only, as the cecum, the hepatic or sigmoid flexure, or the rectum. Generally in fatal cases the large bowel is affected throughout. In some the intestine is riddled with ulcers; in others a moderate number are scattered through it. There appears to be no particular portion of the large intestine that is definitely predisposed to the infection, though the cecum shows ulceration somewhat more frequently than other portions in fatal cases.

The amœbæ insert themselves either between the cells of the normal mucosa, along the interglandular substance, or into small erosions which may exist in the intestine from other causes. They next generally work their way through the muscularis mucosæ by the lymph channels and finally enter the submucosa. Here migration and reproduction take place and infiltration with round cell and œdema results. The mucosa becomes bulged out and small pinhead-sized dots appear on the interior of the bowel. Should a small capillary hemorrhage result in these areas, as frequently happens, the nourishment of the overlying epithelial

cells becomes disturbed, and these, perhaps partly by digestion, become gradually disintegrated, softened, and cast off. The œdematous submucosa is then exposed, which may appear yellowish from infiltration, with round cells or yellowish red if the blood cells still remain in this area. Thus the earliest erosion is formed and becoming exposed to fecal material and bacteria, an increased number of cells accumulate, and if pus cocci are present more or less true suppuration occurs.

The process is limited in extent by the surrounding tissue, which is well supplied with blood and hence red margins to the erosions or ulcerations exist. The amœbæ on the surface die or are cast off into the lumen of the intestine, but others migrate deeper and laterally into the submucosa. Should no hemorrhage occur early beneath the small bulgings of the mucosa, the areas increase in size through the œdema and round-celled infiltration; hence the diameter of these erosions and small ulcerations when first seen depend upon how long the overlying mucosa remains intact before becoming necrotic, disintegrated, and cast off. They therefore generally vary in size from 2 or 3 mm. to about 2 cm. In many of the ulcerations that have originated from nodules which reached 1 or 2 cm. or more in size before opening, we may see evidences of the primary nodular formation from the fact that the margins are raised and thickened and in many cases undermined. Some of the ulcers have a distinct crater-like appearance, with a small opening in the centre, which may be pinhead in size or so large as to freely expose the cavity. The mucosa between the ulcers in early cases may appear perfectly normal, but in later ones a desquamative or hemorrhagic catarrh may be present. The ulcerations increase in size, probably owing to the combined action of both amœbæ and bacteria. The floors and edges become softened, necrotic, and covered with a mucous exudate. In the earlier stages the ulcers are round or oval and placed with their long diameters transversely to the lumen of the intestine. Later they may become irregular in outline. The diameter of the large ones probably depends chiefly upon how laterally the amœbæ have spread out in the submucosa, and their depth mainly upon the depth the amœbæ have penetrated into it before the overlying mucosa was cast off. In the more serious lesions extensive surface ulcerations result whose floors are formed usually of submucosa or deeper ones with smaller diameters whose bases consist of submucosa, muscular coat, or even peritoneum. It is in the ulcerations of moderate depth, owing to the burrowing of the amœbæ in the submucosa beneath the mucosa, that the characteristic undermining of the borders of the ulcers results. This becomes particularly marked owing to the fact that the muscularis mucosæ is not infiltrated and destroyed to the same extent as the submucosa and hence holds up the mucous membrane.

A third form of ulceration sometimes seen is that in which the lesion extends only partially through the mucosa and results from a gradual disintegration of the epithelial cells and not by necrosis and sloughing of the underlying tissues. The bloodvessels of the mucosa are likely here to be more dilated and filled with blood. These ulcers may develop both laterally in the mucosa and in depth into the submucosa; but there

is not in either case the characteristic undermining that is observed in ulcerations of the other type, though the round-celled infiltration in the vicinity is frequently even more extensive. When these surface ulcers extend only into the mucous membrane, amœbæ are rarely found in them, but are sometimes encountered at their margins lying in or between the glands. It seems probable that this form is a direct extension into the mucosa of the process which begins as a hemorrhagic catarrh. It may be due to the action of soluble toxic products of the amœbæ aided later by the intestinal bacteria. A somewhat similar process is observed in the liver, which consists of an extensive necrosis of areas of liver tissue which contain no amœbæ and which are situated in the vicinity of the abscess. Complete breaking down and softening seem to occur only when the amœbæ actually come in contact with the cells, and this may be due to the action of an intracellular toxin.

The amœbæ wandering in the submucosa and carrying with them adherent bacteria cause continuous disturbance. The parasites themselves seem to be responsible chiefly for the œdema and round-celled infiltration, the softening, liquefaction, and breaking down of the tissues. The bacteria cause additional leukocytic infiltration and necrosis. The action of the latter is manifested chiefly in the more superficial ulcerations where the amœbæ may be scanty upon the surface. The parasites in addition cause early infiltration with round cells of the walls of the capillaries and veins, which condition is followed by softening and complete disorganization of these structures. It is in this way that much blood appears in the stools. The amœbæ may penetrate the walls of the veins, and are frequently found inside these vessels, some of which they may have entered directly or been carried from the capillaries through the lumen of the vessel. In this way the veins may become thrombosed. The arteries in the neighborhood of the ulcer also frequently show thrombi, and endarteritis in the chronic process.

In certain cases the tissues seem little able to resist the infection, and large gangrenous ulcers result, the walls of which are soft and the bases of which are formed of blackish or greenish, sloughing tissue in which numerous cocci, bacilli, and sometimes amœbæ are found. These changes are certainly not produced entirely by amœbæ, but are probably due chiefly to the bacteria which are present. Another process is the diphtheritic one. It is also certainly partially if not entirely caused by the action of bacteria.

The process of healing may best be studied in patients who have been under treatment for some time with the intestinal disturbance and in whom death has resulted suddenly from some complication. The ulcers may then be found with bases which are distinctly depressed and have a grayish or grayish-yellow color. Their margins, however, are raised above the bases, and are clear cut but are not usually swollen above the surrounding mucosa. When well advanced toward healing they are no longer softened. The surfaces of the ulcers are bathed in a serous fluid or covered with mucus. Healing takes place by the formation of fibrous connective tissue in the floors and by a gradual covering over with epithelium. If the lesions have been extensive, old pigmented

scars result. Lehman¹ has recently described the intestinal dysenteric lesions produced by amœbæ in horses, cattle, and sheep.

Peritonitis.—The amœbæ may wander freely through the submucosa and into the circular muscular coat, where they are frequently found along the intermuscular septa and between the muscle fibres, which they have evidently separated. The fibres themselves become swollen, granular, indistinct, and may appear without nuclei. They finally become infiltrated, break up, and disappear. The parasites also destroy the bloodvessels in this layer; the blood-supply is then cut off and more extensive sloughs are formed. They may next push along the intermuscular septa through the longitudinal muscle and produce the same changes. Should they approach the serosa similar changes to those seen in the submucosa take place in the subperitoneal coat.

In case many bacteria, particularly the pus cocci, now find their way into the tissue, deep, sloughing, gangrenous lesions are formed and perforation with general peritonitis frequently occurs. In other cases when few bacteria are present this may take place from violent peristalsis after adhesions are formed. However, in the latter instance, particularly when the floor of the ulcer is composed of muscular tissue and does not extend completely down to the serosa, the peritoneal coat, owing to the action of the amœbæ, becomes greatly thickened, not only from the œdema and infiltration but by the formation of considerable fibrin. Occasionally general peritonitis will occur with no visible perforation, the amœbæ having penetrated the muscular coat and serosa and set up an inflammatory exudate which consists of an opaque gelatinous fibrinous fluid in which the amœbæ may be found.

One of the most striking points is the absence of the usual products of purulent inflammation. Polymorphonuclear leukocytes are found in relatively small numbers in the tissues, and are never aggregated together in large groups unless many bacteria are present. The submucosa is very œdematous. Its interstices are widened and the lymph channels engorged. In addition there may be a general liquefaction of the tissues. Extensive round-celled infiltration exists in the submucosa where but few polymorphonuclear leukocytes are usually seen. Plasma cells are present at times in considerable numbers, and eosinophiles are in some cases also fairly numerous. The amœbæ are found in large numbers in the lymph spaces, in which case the endothelial cells in the neighborhood are proliferated and there is sometimes a fibrinous exudate inside the vessel. The parasites are also present in the ulcers, being most numerous in the submucosa along their bases and sides, in the zone of œdema and round-celled infiltration which borders the necrotic portion of the lesion.

Involvement of the lower end of the *ileum* sometimes follows from an extension of the process upward from the cecum. The mucosa just above the valve is frequently hyperemic and occasionally hemorrhagic. In only one of the writer's autopsy series did it show amœbic ulceration.

Lymphatic Glands.—The mesocolic glands are frequently swollen, particularly where the lesions are extensive and extend deeply into the

¹ *Centralbl. für Bakt., Orig.*, 1912, lxii, 589.

muscular coats. They may occasionally be hyperemic or œdematous but are very rarely hemorrhagic, and in this respect offer a strong contrast to the condition of the lymphatics in bacillary dysentery. The lymph sinuses are more or less dilated, and there may be some proliferation of the connective-tissue cells and a few plasma cells present. In rare cases necrosis may take place and bacteria may be present.

The chronic cases sometimes show evidence of parenchymatous *nephritis*, which is rarely of extreme grade. The *spleen* and the *heart* muscle are usually normal, and the *lungs* show no special changes peculiar to the disease except abscess of the right lower lobe, which, together with the lesions of the *liver*, will be discussed under the subject of hepatopulmonic abscess. Abscess of the brain and spleen may also occur.

Symptoms.—These may vary so widely that in order to discuss the subject intelligently the cases may be grouped for convenience under the following divisions: (a) Mild cases and those of moderate intensity. (b) Cases with acute onset. (c) Advanced and chronic forms. This division is purely arbitrary since no sharp lines of distinction can be drawn and the cases may pass from one to the other. Moreover, instances may occur which can be better considered partially under more than one of these divisions. While individual cases may vary widely there are some features which are common in at least the majority. These are the irregular course, marked by periods of intermission and exacerbation, the appearance of mucus in the stools, and the tendency to chronicity. A phenomenon peculiar to the malady is the frequent occurrence of the amœbic liver abscess.

(a) *Mild Cases and Those of Moderate Intensity.*—Usually the patients are not able to tell exactly when they began to realize that they were not in good health. There may be complaint of some lassitude, of becoming easily tired, or of continuous slight headache; more or less indefinite abdominal discomfort, and dyspepsia may be present. Slight intestinal disturbances consisting of moderate diarrhœa or of constipation may appear. Such symptoms may occur singly or in various combinations and are found in patients who, frequently in the tropics among the better classes of people, consult the physician for such minor ailments as have been mentioned and generally have no idea of the real trouble. Such vague symptoms may continue for months, and one may doubt whether they are all dependent upon the intestinal infection. Occasionally the abdominal pains become severer, or there may be an outbreak of diarrhœa which causes the physician to examine the stools, when amœbæ, sometimes mucus and even red blood cells, are found. A great many of these infections remain undiscovered for a long time. Such have been described under the name of latent or masked forms of the disease. Robust men may have the disease for a month or two without being aware that they are suffering from a serious malady. Indeed, some may go to autopsy with advanced intestinal lesions in whom the symptoms have not been sufficiently prominent to attract attention. They may never advance beyond this latent stage; either under some simple treatment by the mouth, or even without treatment, the patient may overcome the infection and the parasites disappear from the stools. In

by far the greater number, however, some of the symptoms sooner or later increase in severity, and in the event of recovery not taking place they may pass gradually into either those of moderate intensity or those with acute onset. The two symptoms most likely to attract attention are *diarrhœa* and *abdominal pain*. In those patients who are constipated the latter may be the first symptom; or indigestion and gradual loss of weight may be equally prominent. Palpation of the abdomen sometimes reveals tenderness, but this is by no means constant. As the lesions in the large bowel increase, the symptoms of intestinal disturbance usually become more marked, abdominal soreness appears, and the stools become more frequent and contain mucus and even blood. If they are properly treated the disease does not usually progress to the chronic stage, and this particularly is why the name "dysentery" is not an entirely apt one for the malady and why "amœbic colitis" would perhaps answer better. The term amœbiasis or more correctly entamœbiasis has been proposed to cover all grades of the infection. Sometimes the abdominal manifestations are so insignificant as entirely to escape notice, or the appearance of a liver abscess first attracts attention.

(b) *Cases with Acute Onset*.—Obviously it is not correct to consider all of these as acute cases. Some are really acute almost from the beginning, but others may have existed for some time as latent, mild, or moderately severe infections. The symptoms are frequently not in accord with the lesions; ulcerations may exist and become well-marked before there is a sudden outbreak of the diarrhœa. Very abrupt onset may occur from the formation throughout the large intestine, but particularly in its lower portion, of very numerous small and superficial ulcerations, or from secondary infection with streptococci or *Bacillus dysenteriae*. Cases with diphtheritic or gangrenous lesions may be classified clinically under this division, and in the latter instance portions of sloughing tissue may be passed in the stools. At the onset there may be from 15 to 50 or more bloody mucous movements in twenty-four hours. A high leukocytosis is frequently present. Colicky pains in the abdomen with tenesmus occur; fever, nausea, and vomiting may appear; great exhaustion sets in; the heart action becomes feeble and death results, or the condition temporarily improves and gradually assumes the chronic form. It is in this form that wild delirium may appear before death.

(c) *Advanced and Chronic Cases*.—In the advanced stages the symptoms become well-developed. The movements become more frequent and usually contain much mucus and frequently blood. Their number may vary from 2 or 3 in the morning to 10 or 15 or more during the day. There is aching in the back, and at times sudden and intense desire to defecate. As the disease becomes chronic, loss of weight is progressive, and finally marked emaciation may result. The patient becomes anemic and the muscles soft; the tongue is pale and moist at first, later slightly furred, or sometimes heavily coated. There is more or less anorexia; indigestion and flatulence are common. The pulse and respirations may be slightly increased. The temperature is normal or subnormal in the morning and slightly elevated in the afternoon. As the malady

progresses the anemia becomes more marked, the skin dry and dull yellow in color, and the face drawn. The emaciation in some cases becomes very extreme; the abdomen becomes sunken, bed-sores may appear, and death follows from exhaustion or terminal infections. Another type of the chronic form is that in which there is nothing more than an intermittent diarrhœa often alternating with constipation, and accompanied, usually, by slow but gradual loss of flesh. These patients sometimes remain in this condition for several years. Occasionally the parasites disappear and the more serious lesions heal, but the bowel never assumes again its normal condition. Where the destruction of tissue has been extreme, cicatrices form and a chronic catarrh remains.

The *course* is very variable and is not self-limited. The grave cases with acute onset may terminate fatally within a week or ten days in spite of all treatment. The mild and moderately severe ones may continue for many months before alarming symptoms appear. The occurrence of complications may terminate the infection in death or completely alter its course. If proper treatment is instituted many of the mild and moderately severe cases recover entirely, and the parasites disappear within one to six weeks. Some of the chronic ones are completely restored to health within two to three weeks, but, on the other hand, convalescence may be delayed for three to six months. Occasionally amœbæ persist after all symptoms and sometimes the lesions themselves have disappeared; the cysts may persist for long periods after convalescence. Complete recovery is sometimes doubtful owing to the fact that after many weeks of apparent cure patients may develop more acute symptoms; sometimes these represent fresh infection, but usually they are merely evidences of the outbreak of the original disease. Cases of this nature, unless treatment is pursued until complete recovery results, are apt to suffer with so-called relapses every few weeks or months until some grave complication carries them off. Patients who do not recover under continuous treatment for six or eight months are likely either to die within a year or linger on as incurable.

Death may occur from the gravity of the intestinal lesions, from exhaustion in protracted cases, from severe complications, from a terminal infection, from intercurrent diseases, or from severe intestinal hemorrhage. The severity of the intestinal lesions and abscess of the liver are the most frequent causes of death.

Gastro-intestinal Symptoms.—Of these, diarrhœa is the most important, usually being intermittent, coming on abruptly, and subsiding in like manner. Between the attacks the stools may become formed. The intermissions may last several weeks or even months, or diarrhœa may be absent throughout the entire course. The character of the diarrhœa usually depends, first, upon the ulceration, whereby increased peristalsis results, probably owing to the nerves being eroded and exposed; *second*, upon the impaired power of absorption of water by the intestine, due in part to the marked œdema. Ulcers of the intestine can exist without any diarrhœa, as is particularly likely when they are superficial and in the cecum or the adjacent portion of the ascending colon. When the

ulcers are very numerous throughout the intestine, or well-developed in the descending colon and rectum, diarrhoea is practically always present. In mild cases the movements may not exceed 3 or 4 in twenty-four hours, but in the gangrenous and diphtheritic forms the diarrhoea becomes excessive and the movements sometimes number 50 or more in this time. In fatal cases before death they may diminish to 2 or 3. This has been explained as due to the gradual loss of expulsive power caused by the destruction of the muscular coat and nerves situated in the ulcerated areas, and the general oedema of the bowel wall.

Feces.—The stools vary greatly in different stages and in different cases. Valuable information may be obtained from them of the condition of the lesions in the intestine and of the progress of the disease. At times they are liquid, at times pultaceous, and again well-formed. In color they may be brownish, greenish, reddish, grayish, or variegated. In cases with gradual onset they are likely at first to be merely more or less watery and of normal color. As the lesions develop, mucus begins to appear. In the cases with marked intestinal catarrh and extensive ulceration it is always more abundant. The mucus may be finely divided, shreddy, and mixed throughout the stool, or it may appear in large masses. The latter condition is particularly likely to exist when the feces are well-formed, when small portions of blood-stained mucus may be observed over the surface of different portions of the stool. At times the movements consist of masses of blood-stained mucus.

Blood may be present so that the color of the whole mass is modified, or as clotted masses in portions of the stool, or mixed with mucus. It is sometimes in such small amounts as to be apparent only upon microscopic examination; or the stool may consist entirely of blood mixed with mucus. It is probable that the amount of blood is partially dependent upon the rapidity with which the lesions are forming as well as upon their position and extent. The presence of considerable blood in the stool makes the diagnosis of ulceration very probable; but we cannot conclude in its absence that ulcerations do not exist. When the ulcerations are high up in the cecum the blood is apt to be altered and brownish or even blackish in color.

Pus cells are found chiefly after ulceration is well-developed and in the diphtheritic form of the disease. In the chronic cases it is not unusual to find large numbers of polymorphonuclear leukocytes. Small round cells are usually very abundant where a well-developed catarrhal condition exists and where epithelial cells are also numerous. When pus is found in considerable amount it is an almost certain indication of extensive ulceration.

Shreds of Tissue.—As ulceration advances and becomes more chronic the amount of blood grows less; the stools become more copious and again more watery; fragments of tissue are frequently seen in the early stages of the chronic cases. In advanced and particularly in gangrenous cases large sloughs and sometimes complete moulds of the intestine are cast off.

The reaction of the stools is generally alkaline, sometimes neutral, and occasionally acid. In instances of recovery the mucus is the last

abnormal element to disappear from the feces. It usually persists for a long period and in many cases it never disappears.

Microscopic examination reveals the amœbæ in addition to those elements which have been described. These may be very plentiful or scarce, the number depending upon several factors. If there are only a few ulcers in the large intestine the mucus and feces that have come in contact with these lesions are likely to contain the parasites in the largest number, and they will probably be scanty elsewhere. If the stool is liquid the organisms will be more or less evenly diffused throughout. The gravity of the lesion is not always indicated by the number of amœbæ found. With very advanced lesions when the parasites are burrowing deep in the submucosa there may not be as many as in more acute conditions. Numerous epithelial cells, small round cells, pus cells, eosinophiles, and a fair number of Charcot-Leyden crystals are also frequently found. Bacteria are usually increased beyond those in normal stools.

Abdominal Pain.—This is very variable and occurs more acutely in the gangrenous cases and when perforation is imminent. It may be colicky and very severe, localized over a particular ulcer, or exist over the abdomen generally. In chronic cases a dull, aching pain with occasional sharp exacerbations may be present. When this is constant, limited to a fixed point, and increased by external pressure, it is suggestive of the site of ulceration, although extensive ulceration may exist without any pain. Pain which is produced only by external palpation and pressure suggests areas of circumscribed peritonitis. Very excessive pain on pressure is usually present when the serosa itself is involved. If widespread or extensive ulcerations are present, pain on pressure may be elicited along the whole course of the large intestine. Cramp-like and aching pains frequently occur before and after evacuation of the bowel. A feeling of abdominal heaviness is not an uncommon symptom and is frequently accompanied by distension and flatulence. *Tenesmus* is not nearly so marked or frequent a symptom in uncomplicated amœbic dysentery as in the bacillary form. It is most evident in the grave cases and in the gangrenous and diphtheritic forms, where the sigmoid flexure and rectum are involved. In the remaining cases it depends chiefly upon the extent of the ulceration in the rectum. A burning sensation in the anus after defecation is frequently present.

Nausea and vomiting of severe grade are somewhat rare but may occur early in the cases with acute onset. In moderate form they are most commonly encountered in the chronic ones. Nausea sometimes develops as a result either of prolonged treatment with ipecac or of the large and high enemas administered for treatment.

Loss of appetite is a common symptom and is almost absolute in the acute cases. In the moderately severe ones it may not be apparent, but it becomes very evident again in the chronic cases.

Hiccough is seen in the grave forms shortly before death and when the peritoneum is involved. The *tongue* shows nothing that is characteristic. In instances of very long standing it is likely to become fissured and to show small hemorrhages and erosions along its sides and tip.

Anemia of a secondary type is present in all the cases of long standing and is progressive with the disease. It is dependent chiefly upon the loss of blood from the intestinal lesions and the gastro-intestinal disturbances. It is possible that it may be in part of toxic origin due to absorption. The reduction in hemoglobin is usually greater than that of the number of the red cells; the hemoglobin varies generally from 50 to 80 per cent. Fitcher's average for the red cells in 38 cases was 4,802,000. In the tropics, in the advanced and chronic cases, the red-blood cells sometimes are not over 2,500,000. There is frequently a slight leukocytosis, and a marked one is sometimes found in the very severe cases when the polymorphonuclear cells are usually increased. The eosinophiles are not increased in cases uncomplicated with other intestinal parasites.

The *skin* is normal in the mild and moderately severe cases. In the chronic ones it becomes dry and sometimes glazed, and assumes a sallow, yellow appearance when the mucous membranes show distinct pallor.

Fever.—The temperature is likely to be elevated in the cases with acute onset; it is generally higher in the diphtheritic form, and particularly when complicated with *Bacillus dysenteriae*. In the mild and moderately severe types there is usually little or no fever. In the chronic ones the temperature is frequently subnormal for a portion of the day with afternoon rises of 100° to 102° F. At other times it may be subnormal or normal for a week or more. In cases with many streptococci in the stools and advanced lesions of the intestine, it may become septic with daily rises to 103° to 104° F. Fever becomes an important symptom in perforation and in abscess of the liver and lung, when it is sometimes accompanied by rigors and sweating.

The *pulse* and *respiration* are apt to be increased if fever is present. The pulse is frequently rapid in the grave cases with acute onset, and may become thready and rise to 120 to 140 or more. Usually in cases of moderate severity it is not over 100, and in the mild and chronic cases it may be normal. The respirations are increased particularly in abscess of the liver and lung.

Urine.—Moderate albuminuria accompanied by a few hyaline casts is occasionally seen in chronic cases. The urine is then usually somewhat reduced in amount. Harris noted that in the severe forms the chlorides are often diminished and that in the most severe instances they may be entirely absent. Retention sometimes occurs when acute symptoms of dysentery are present.

Complications.—**Abscess of the Liver.**—This is the most frequent and one of the most serious complications. In 119 cases reported by Fitcher it occurred in 22 per cent.; in a series of 100 cases examined at autopsy by Musgrave and the writer in 23 per cent.; in 74 by Craig, 33 per cent.; in 57 by Kruse and Pasquale, 11 per cent.; in 95 by Harris, 15 per cent. In India, in the British Army, Rogers found one case of liver abscess to every seven of dysentery. It is much more common in males than in females. Rouis in Algiers found that of 258 cases 3 per cent. occurred in women. The Indian statistics regarding families connected with the army gave a sex ratio of about 7 males to 1 female.

Fletcher reported 3 cases in women in his series. Natives in the tropics are much less liable to infection than Europeans. Havelock Charles¹ found that in India the death-rate from liver abscess was 21 times higher in British troops than in the native army. It is generally a complication of adult age. In the series of 28 cases reported by MacCallum² none of the cases occurred in individuals under twenty-one years of age.

Harris and others state that this complication always arises during the acute period but observations show that it may develop at any time, and certainly not uncommonly after all symptoms of dysentery have ceased, or indeed, sometimes before any intestinal ones have developed. In some of the fatal cases there have been no evidences of intestinal lesions and no history of dysentery. However, in the majority the abscess becomes evident in the first month after the onset of the dysentery. The most common seat of the abscess is in the upper and posterior portion of the right lobe. Out of 639 cases of abscess in amœbic dysentery collected by Rouis, 70.8 per cent. were situated in the right lobe and 13.3 per cent. in the left lobe. In Charles' cases in India 85 per cent. were in the right lobe. There may be single or multiple large abscesses or very numerous small ones scattered throughout. Waring found in 300 cases 177 solitary and 108 multiple abscesses. Niblock reported from Madras the abscess single in 83 per cent. and multiple in 17 per cent. In Fletcher's series out of 18 cases, 10 were single. In the writer's series, 13 were single and 10 multiple. The number of abscesses is obviously an important factor from a surgical standpoint, the cases with multiple abscess being more fatal.

For a long time alcohol has been believed to predispose to liver abscess and play an important part in its etiology. In 12 cases among private patients, 8 were alcoholics. In the Philippine Islands at least, malaria is generally not a predisposing factor. Kartulis has reported 6 cases of liver abscess with amœbic appendicitis. In 3 the intestinal lesions were most marked in the cecum and appendix.

The amœbæ are supposed to reach the liver by two paths. The more common is certainly through the portal vein. Amœbæ are frequently found in the veins of the submucosa and in the portal capillaries. The other method of transmission is through the peritoneal cavity. Councilman and Lafleur and Rogers all support this theory and think that infection occurs in many cases in this manner. The parasites are supposed to migrate through the intestinal wall and then invade the liver from its surface. Lafleur has cited an instance with peritonitis present in which amœbæ were found over the peritoneal surface of the intestines and liver. This would certainly seem to be one mode of infection. In one of the writer's cases an amœbic abscess occurred beneath the right rectus muscle, the infection apparently having entered through the parietal peritoneum. In another the abscess was less than a centimeter in diameter, solitary, and just beneath the surface of the right lobe.

Character of Amœbæ in Liver Abscess.—In general the amœbæ encountered in the abscess are similar to the parasitic species found in the

¹ *British Medical Journal*, 1908, ii, 1235.

² *Mense, Handbuch der Tropenkrankh.*, iii, 22.

intestine in dysentery. Noc¹ and Liston and Martin² have cultivated amœbæ from liver abscesses and the latter authorities believe that two distinct species have been isolated.

Bacteriology.—In addition to amœbæ the abscesses are often infected with bacteria. In 27 cases reported by Fitcher and examined bacteriologically, 15 contained bacteria; of the writer's 23 cases bacteria were found in 13, and in 37 of Rogers' they were present in 16. In the larger abscesses the bacteria may have died out, but a proportion of even the earlier abscesses seem to be entirely sterile. The organisms most frequently found are the staphylococcus and the *Streptococcus pyogenes* and the colon bacillus; the *Micrococcus lanceolatus* and the *Bacillus pyocyaneus* have occasionally been reported. It is obvious why bacterial infection occurs so frequently, as these organisms have the same opportunity for entering the liver as the amœbæ and frequently adhere to them. Undoubtedly the pus cocci exert an injurious influence upon the hepatic tissue, but there can be little doubt that the amœbæ play a most important part in the formation of the abscess. This is demonstrated by the very different character of the amœbic and the pure bacterial variety. The contents of the former vary somewhat. In the smaller abscesses they consist of thick, glairy, yellowish masses of mucus which are not fluid. In the large abscesses the contents are more liquid, frequently like thick gruel, and yellowish, grayish red, brownish red, or at times greenish in color. Frequently shreds of necrotic liver tissue are mixed with the fluid portions. Microscopically one is struck usually with the absence, or presence in small numbers only, of polymorphonuclear leukocytes. The contents consist mainly of fine or more coarsely granular material containing fragments of cells, many swollen and fatty degenerated liver cells, red-blood corpuscles, fat globules, and amœbæ. The latter are sometimes difficult to find in the pus, but can almost invariably be obtained in scrapings made from the abscess wall, though sometimes repeated examinations are necessary to detect them.

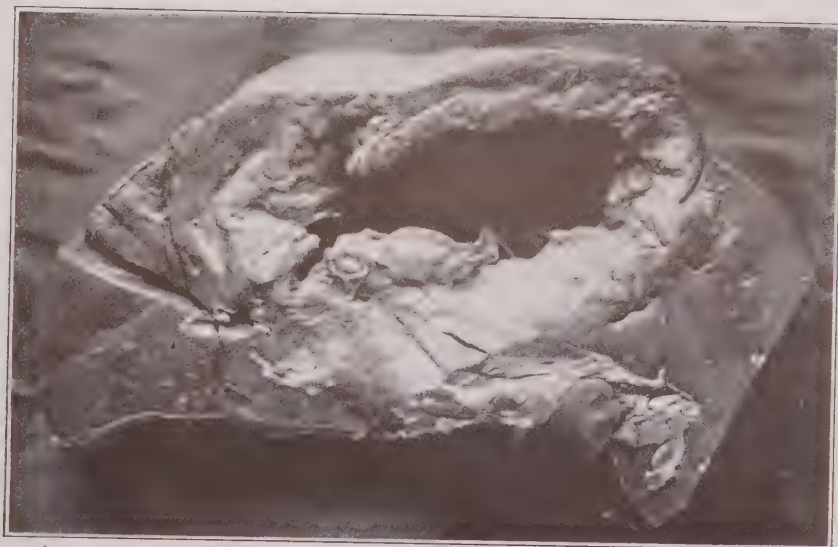
Special Pathology.—The liver may be of normal size, but is frequently enlarged. The tissue often shows advanced fatty degeneration or chronic passive congestion, or, sometimes, it is acutely congested. There are areas of localized peritonitis where the abscesses reach the surface of the liver, and the overlying tissues may then be bound by adhesions to it. The size of the abscesses may vary from several millimeters in diameter to that of a man's head. Very frequently several abscesses about the size of an orange are encountered. A somewhat rarer condition is that in which very numerous small abscesses are scattered throughout both lobes of the liver. The older abscesses usually have walls composed of a dense layer of fibrous connective tissue. The edge of the abscess consists of a necrotic area of liver cells where the amœbæ, together with leukocytes, blood corpuscles, and fibrin filaments, are frequently found. The capillaries are dilated, filled with blood, and frequently contain the parasites. The latter show no indication of attempting to penetrate beyond the necrotic zone. Outside this layer is a zone in which great

¹ *Annals de l'Institut Pasteur*, 1909, xxiii, 180.

² *Quarterly Journal Microscopical Science*, 1911-12, lvii, 107 and 122.

PLATE IV

FIG. 1



Large Single Amoebic Liver Abscess.

FIG. 2



Hepatopulmonary Amoebic Abscess

activity of the connective-tissue cells is observed and in which the liver cells are frequently compressed and atrophied; mononuclear small cells are usually abundant. Finally, this layer is usually surrounded by a zone of more marked hyperemia where small hemorrhages are frequent. In these latter areas thrombi may occur in the branches of the portal veins, where amœbæ and bacteria may both be found. Councilman and Lafleur have also described a widespread necrosis of the cells situated round the central veins of the lobules and scattered throughout the liver. They suggested that this is due to soluble chemical products of the amœbæ. A striking point also observed is the absence of leukocytic infiltration, which usually accompanies suppuration of bacterial origin. For a more detailed description of the histological lesions, the reader is referred to the excellent monograph of MacCallum.¹ (Plate IV, Fig. 1.)

Diagnosis and Symptoms.—Liver abscess is frequently overlooked, and this is not strange, for sometimes its development takes place so insidiously that perforation may be the first indication. If the onset is more acute the diagnosis is simplified. The more frequent indications are fever, functional disturbances, progressive enlargement, and pain. *Pain* is very common at some time. It is commonly dull and aching, but may become sharp and lancinating. Its situation varies greatly, being almost as frequent in the vicinity of the right scapula and shoulder as over the liver itself. In the former case the pain is, according to Fitcher, reflex through the phrenic nerve which receives large branches from the fourth cervical. The pain may occur over the hypochondrium or epigastrium. When not present spontaneously it may be elicited upon pressure over the liver. However, pain is not constant, and is frequently absent. *Fever* is usually present at some time, but is often not sufficient to attract attention. Occasionally it is continuous and not over 100° to 102° F. In other cases it is remittent; or it may be septic in type and intermittent and rise in the evening to 104° F. Chills and sweats may then occur, and the symptoms simulate those of malaria. Lafleur calls attention to sweating as an important symptom, and states that it is independent of the temperature. The pulse may be little increased, but in the cases with high fever it may be 140 or more. There may be a spasmodic, hacking cough usually worse at night. It, however, is not peculiar in any way to liver abscess.

Blood.—There is usually a leukocytosis from 15,000 to 40,000 in which the polymorphonuclear cells are the variety increased. However, the leukocyte count may be normal. A very high polymorphonuclear leukocyte count usually occurs when infection with bacteria is also present. Before actual suppuration has occurred the large mononuclear cells may be the variety increased. Mathés and Leger in 27 cases found the eosinophiles reduced to generally less than 1 per cent.

The conjunctivæ are sometimes slightly tinged with yellow, but marked jaundice is rare. Persistent vomiting may occur. The skin frequently assumes a sallow color, and the face may become pale and yellow. The facies may suggest the diagnosis. In certain cases emacia-

¹ *Handbuch. der Tropenkrankh.*, 1906, iii, 22

tion occurs rapidly; in others the flesh is well retained. The appetite usually disappears and the tongue becomes coated. Physical examination may show enlargement of the liver, which may even cause bulging on the right side; pain may be elicited on pressure. Occasionally a swelling may be observed over the sixth and seventh ribs. The movements of the right side of the chest during respiration may be limited. Percussion and auscultation frequently give no information of the condition. If the abscess is large, percussion may reveal an increase in hepatic dulness. A friction rub may be heard over the liver when the peritoneum is involved. When considerable destruction of hepatic substance has taken place the *urea* excretion may be diminished. In a case reported by Rolleston crystals of leucin and tyrosin and cholesterin were present in the urine for ten weeks. On opening the abscess the urine became normal. Albuminuria is sometimes present. Pel¹ calls attention to the dysphagia in some cases which may simulate carcinoma. In the diagnosis of liver abscess there is not a single symptom that is constant, and proof that the liver is involved may be very doubtful. The general condition and appearance of the patient, with the progress of the case, rather than any single symptom, often suggest the diagnosis, which may sometimes be confirmed by aspiration.

Spontaneous rupture of amœbic abscess frequently occurs if the patient lives long enough and is not operated upon. This is most often into the lower lobe of the right lung. Rupture into the abdominal cavity causing general peritonitis is also frequent. The abscess may perforate into the pleura, pericardium, stomach, colon, small intestine, bladder, vena cava, kidney, and through the skin in the lumbar or right hypochondriac region. Dagorn and Heyman² described a case of liver abscess which had been operated upon in which a small cutaneous abscess developed near the wound and in the pus of which numerous amœbæ were found. Carini³ has also described the occurrence of amœbæ in the gangrenous subcutaneous tissue of a liver abscess case.

Abscess of the Brain.—Kartulis has reported⁴ brain abscess as occurring in 3 per cent. of his liver abscess cases. Amœbæ were sometimes found in the vicinity of the necrotic areas. Jacob,⁵ in 1911, collected 9 cases and Legrand,⁶ in 1912, 45 cases from the literature. Europeans were most frequently affected; 26 of the cases occurred in Egypt; with 4 exceptions the patients were between twenty and forty years of age; one case occurred in a girl of five and one in a boy of fourteen; only 3 were in females. This complication occurs almost exclusively as an accompaniment of abscess of the liver, though the symptoms due to it may not appear until the liver lesion has become quiescent or has been cured. The abscess is usually single but may be multiple. It occurs most frequently in one of the hemispheres and may rupture into the ventricle and cause acute symptoms. Meningitis occurs only exception-

¹ *Krankh. der Leber*, 1909, Jena, Gustav Fisher, page 140.

² *Bull. Soc. Méd. Chir., de l'Indochine*, 1912, iii, 518.

³ *Bull. Soc. Path. Exotique*, December 1912, p. 799.

⁴ *Centralbl. für Bakt.*, 1904, xxxvii.

⁵ *Presse Médicale de Égypte*, 1912, iv, 309.

⁶ *Revue de Chir.*, xxvi, 662.

ally and hence lumbar puncture yields a clear fluid. The symptoms are not different from those of cerebral abscess in general. The toxic evidences of suppuration are not prominent and there is almost no evidence of intracranial tension.

Abscess of the spleen may occur but is very rare. Kartulis¹ observed but one case as a complication of amœbic dysentery and no amœbæ could be found in the pus. Rogers² has recently reported a case in which the spleen was enlarged, and upon exploration eight ounces of thick, reddish pus were withdrawn. Jurgens reported two cases of thrombosis of the femoral vein in one of which amputation of the leg was necessary. *Pericardial abscess* has also been observed. In two instances reported by Kartulis a perforation of an abscess of the left lobe of the liver through the diaphragm into the pericardial sac occurred.

Abscess of the Lung.—Preceding this, the respirations are usually increased in number and are often painful and shallow. Before perforation occurs the signs of pleurisy are usually present. Cough and expectoration then appear, and are generally constant. The cough in the early stage is hacking and accompanied by pain over the liver. When the abscess discharges into the pleural cavity or into a bronchus, the dyspnœa becomes less marked. Sooner or later the characteristic anchovy-sauce sputum appears, in which can be found amœbæ with red blood corpuscles, leukocytes, altered liver cells, alveolar epithelium, elastic-tissue fibres, Charcot-Leyden, tyrosin, and hematin crystals, and various bacteria. Small, cheesy particles consisting of granular material and oil drops are also encountered. (Plate IV, Fig. 2.)

Special Pathology.—In abscess of the lung the diaphragm is adherent to the liver and usually to the base of the lung. If the latter is not the case, a layer of pus separates the lung from the diaphragm. Abscesses are never metastatic, and the lower right lobe is affected. The diaphragm may or may not be visibly perforated. On opening the lung abscess it may be found filled with viscid, yellowish-gray or yellowish-red, partially fluid material; or, if perforation into a bronchus or the pleural cavity has occurred, it may be empty. Sections of the older abscesses show usually three zones; first a necrotic one containing fragmented nuclei, degenerated cells, and amœbæ; second, a layer composed of connective-tissue fibres, epithelial cells, elastic fibres, sometimes distinct groups of air cells, and occasionally amœbæ; and third, a layer of small round-celled infiltration in which fibrin and some proliferation of the connective-tissue fibres is also visible between the air cells. The walls of the bronchi are thickened and infiltrated with numerous round cells. The bronchi contain either purulent or serous fluid.

Hepatopulmonary abscess is a somewhat rare condition, although in Kartulis' series lung abscess and pyothorax occurred in 8 to 10 per cent. of his liver abscess cases. Harris reports it 3 times in 95 patients, and Fletcher 9 times out of 119 with 3 cases in which the liver abscess ruptured into the pleural cavity. In the writer's series of 100 fatal cases,

¹ *Handbuch Pathogenen Mikroorganismen, Kolle und Wassermann, 1907. Erster Ergänzungsband, page 381.*

² *British Medical Journal, 1912, ii, 403.*

hepatopulmonary abscess occurred but once with 2 cases of empyema. Lung abscess does not always occur from perforation of a liver abscess into the lung. When rupture into a bronchus takes place, the condition may last from six to eight weeks and terminate in death or recovery, or persist for a year. The mortality is usually very high.

Peritonitis.—A local peritonitis may result from extension of the ulceration in the bowel or from an abscess in the liver. Patches of fibrous adhesions are frequent; in chronic cases it is the rule to find old localized areas of chronic adhesive peritonitis. They may cause abdominal soreness and pain. Peritonitis, which generally proves fatal, may follow perforation of a liver abscess or an intestinal ulcer.

Perforation of the intestine results generally from the giving way of the base of a deep sloughing ulcer and is most frequent in the grave and gangrenous cases. The opening is usually a large one. The perforation occurs frequently in the cecum, and the condition has sometimes been mistaken for one in which the appendix is involved. Perforation of the large bowel with general peritonitis occurred in 19 of the writer's 100 autopsies. In 2 other cases it occurred after the ulcer was thoroughly walled off from the peritoneal cavity. In Fletcher's series, perforation occurred only in 3 and in Craig's in 4 cases. In the writer's series of 200 clinical cases it occurred but 3 times. It is almost invariably fatal. Death may occur in a few hours from shock, or later from the resulting acute general peritonitis. Perforation sometimes happens after adhesions have formed, when a pericecal or pericolic abscess may result. It may take place retroperitoneally into the psoas muscle and may even open externally.

Appendicitis.—This complication occurred in 7 of my 100 fatal cases. In one a chronic appendicitis existed in connection with a pericecal amebic abscess. In 4 of the 6, death resulted from general peritonitis following perforation of the cecum or colon. All showed extensive general intestinal lesions and the involvement of the appendix merely followed extension from the cecum. A definite diagnosis of the appendicular affection during life is very difficult, since the cecum in addition is usually extensively diseased. The process is not very acute as a rule.

Intestinal Hemorrhage.—Intestinal hemorrhage in which large amounts of pure blood are passed from the rectum is a rare complication. In 1902, the writer called attention to severe intestinal hemorrhage as a fatal complication and reported 2 cases in both of which liver abscess was present and in which death was due to severe multiple hemorrhages. It was suggested that these large hemorrhages might perhaps bear some relation to the condition of the liver. Haasler reported from China 3 instances of intestinal hemorrhages, in 2 of which death took place from bleeding. In both of these cases liver abscess also existed. Since this time the writer has seen 2 more fatal cases from multiple hemorrhages, both with liver abscess, and reports of other similar cases have been made since. Therefore a connection between intestinal hemorrhage and the hepatic condition is suggested. While it is probable that fatal intestinal hemorrhage may occur independently of liver abscess, the cases mentioned suggest that when hemorrhage occurs in patients with

liver abscess it is likely to be very severe and the bleeding is likely to recur. Fitcher reports intestinal hemorrhage in 3 of his series.

The frequent occurrence of small amounts of blood in the stools may be explained from the fact that the walls of the veins are early infiltrated with round cells, followed by softening and complete disorganization, also from the fact that amœbæ may penetrate the walls of a vein. However, thrombosis of the veins is not infrequent.

Sequelæ.—In chronic cases with extensive ulceration large cicatrices frequently form. When a long-continued catarrhal condition has been present a general atrophy of the mucosa may take place. In these instances we sometimes find a clinical condition closely resembling *sprue* or *psilosis*. The small intestine, owing to the inanition, anemia, etc., may also become secondarily involved and its mucosa atrophied. The stools then are copious, liquid (at least never formed), pale in color, and usually frothy. The chronic gastric catarrh and enteritis, which frequently develop with a sore and fissured tongue and often an inflamed œsophagus, complete the picture. This condition was observed in 3 very chronic patients who finally overcame the amœbic infection.

Diagnosis.—This is not difficult by microscopic examination; but there are other forms of dysentery which clinically it may be impossible to distinguish, and one who attempts to make a diagnosis from the clinical manifestations alone will make frequent mistakes. The occurrence of amœbic liver abscess always confirms the diagnosis, but sometimes the symptoms to which it gives rise are the first ones to attract attention to the intestinal disease. The examination of the stools should be made as soon as possible after they are passed, and the specimens should be collected free from urine. Many observers recommend in cold climates that a warm bed-pan be used and that the microscopic slide be gently warmed. This is not necessary in tropical countries. These precautions are necessary because the amœbæ frequently die in stools that have stood for any length of time or that contain urine, and their motility is often quickly impaired by cold; motile and resting amœbæ also quickly disintegrate in cold stools. The amœbæ must be found living and motile. In this condition they are easily recognized and cannot be mistaken for other cells. After movement ceases and death results, it is frequently impossible to distinguish them from other substances. If bloody mucus or small pieces of necrotic tissue are present, these should be examined first, for if they come from the neighborhood of an ulcer they usually contain very large numbers of amœbæ. If the movements are not liquid a dose of Rochelle salts should be given and the fluid portion of the stool examined. Another very convenient method of securing material for examination is by the passage of the rectal tube. When the stools are fluid considerable amounts may be obtained, or small portions of mucus will be found in the lumen of the tube.

The differential diagnosis between *Entamœba coli* and *entamœba* of the *histolytica*, or *tetragena* type, is important, but is frequently very difficult. If eight nuclear cysts are found present in the stools, the presence of *Entamœba coli* is assured. But the finding of these cysts does not exclude the possibility of infection at the same time with

Entamæba histolytica or *tetragena*. If the cysts contain four nuclei or less, the differentiation is more difficult. If on repeated examinations the cysts never contain more than four nuclei, the diagnosis of the tetragena species can usually be made with safety. It should be recalled that while the trophozoites are present in the active stages of the dysentery, cysts of the pathogenic amœbæ are frequently not found present except in the quiescent stages of the disease, in convalescent cases, or in those which have recovered, and that the cysts of *Entamæba coli* may be encountered only when the stools are formed. The cysts usually only develop in the intestinal tract and not in the stools. When the process begins in the intestine, it may be completed in the feces, and the process of partial development observed if the specimen is placed in a moist chamber. In the trophozoite stage the diagnosis of the species is much more difficult, but may be made usually from the differences which exist in the character of the ecto- and endoplasm and in the relationship which exists between them and by the character of the nucleus. The morphological details of the nucleus can only be distinguished in hardened and stained preparations. The preparations for staining must be prepared from perfectly fresh stools and fixed when moist. Hot alcoholic solution of mercuric chloride (one part absolute alcohol, two parts saturated solution mercuric chloride) may be used in fixation, the specimen afterward being washed in 50 and 70 per cent. alcohol and then in iodine alcohol solution. After hardening for about fifteen minutes in 80 per cent. alcohol, the specimens should be stained in dilute aqueous alum hematoxylin for several hours.

Not all protozoölogists are in agreement in regard to the points of differentiation in the human intestinal species. Walker, who has had in my laboratory in Manila during the past few years a wide experience in the diagnosis of these species, emphasizes the following points of differentiation: "One of the species is characterized by its porcelaneous and refrangent appearance, distinct nucleus and sluggish motility, in the living entamœba; by the deeply staining, granular cytoplasm, and by the relatively large amount of chromatin, which is arranged either as a heavy, continuous, or broken ring (*coli* variety) or as several discrete masses (*nipponica* variety) on the inner surface of the nuclear membrane, with transitions between these two varieties, in the stained entamœbæ; and especially by the development of cysts containing eight nuclei. This species should, according to the law of priority, bear the name of *Entamæba coli* Schaudinn. It is found in the stools of healthy persons and of persons suffering from diseases other than dysentery and is, therefore, presumably non-pathogenic. The other species includes the histolytica variety of Schaudinn, the tetragena variety of Viereck and Hartmann, and probably the minute variety of Elässian. It is characterized by its hyaline and feebly refrangent appearance, indistinct nucleus, and active motility in the living entamœba; by the feebly staining reticulated cytoplasm, and by the relative paucity of chromatin which is arranged either as a barely perceptible layer about the inner surface of the nuclear membrane with or without a few fragments scattered in the nuclear net-work (*histolytica* variety), or as a more extensive but

loose, granular peripheral layer and a loose central karyosome (tetragena variety), with transitions between these two varieties in the stained *entamœba*; and especially by the development of cysts containing four nuclei. This species is found only in the stools, pus, or tissues of cases of amœbic dysentery, amœbic liver abscesses, or of cases having a history of amœbic dysentery, and is probably a pathogenic species. According to the law of priority this species should bear the name *Entamœba histolytica* Schaudinn."

Whitmore¹ is not in agreement with Walker in regard to the type of intestinal amœba most commonly encountered in Manila, believing that only *Entamœba tetragena* is encountered there. Hartmann² concludes that the *Entamœba tetragena* may on many occasions have no distinct ectoplasm so that it comes to resemble *Entamœba coli*; and that in order to distinguish the two it is necessary to consider other points of differentiation such as the nuclear condition and method of reproduction. Darling³ recommended that for the differentiation rectal injections be made in kittens with fresh material containing trophozoites and then stained preparations be studied of the developmental stages which take place in the intestine of the animal. Sellards,⁴ working in my laboratory, has recently shown that biological distinctions may be demonstrated by the employment of specific sera, cytolytic for the different species of amœbæ.

Infection with other diseases may coexist, and in cases with acute onset it will be important and advisable to make plate cultivations of the bacteria from the stool and search for *Bacillus dysenteriæ*, as well as test the agglutinative and bactericidal reaction of the patient's blood serum with this organism.

The diagnosis of *liver abscess* should be made only after a careful consideration of all existing symptoms. The general condition of the patient and his feces together with the progress should be taken into account. The blood should be examined to exclude malaria and for a leukocytosis, but it must be remembered that the leukocyte count may occasionally be almost normal. Rogers⁵ believes that a presuppurative stage may be recognized when a marked leukocytosis is present and there is little or no increase in the proportion of polymorphonuclear leukocytes. Radioscopic examination should be resorted to in cases of doubt. If abscess is present the right side of the diaphragm may be moved upward, and frequently it does not move as readily as the left side during respiration, though as Da Costa⁶ has pointed out, paralysis of the diaphragm rarely occurs in abscess of the liver and respiration is not much affected unless the diaphragm of that side and the pleura become involved. If no intestinal disturbance exists, an additional clue may be obtained from the history or by finding the amœbæ in the stools. An absolute diagnosis can frequently only be made by the finding of amœbæ in the abscess. This may sometimes be done by aspiration. A needle having

¹ *Centralbl. für Bakt.*, 1911, Part I, Jena, lviii, Orig. 234.

² *Archiv für Protistenkunde*, xxiv.

³ *Bull. de la Société de Patho. Exotique*, 1913, vi, 149.

⁴ *Philippine Journal of Science*, 1911, vi, 281.

⁵ *Practitioner*, June 1907, p. 776; also *Fevers in the Tropics*.

⁶ *Modern Surgery*, 1910, p. 1020.

a sufficiently large calibre to transmit the thick pus should be used. The puncture may be made through the skin, the point of entrance being over the suspected area; but the surgeon must be at hand to operate if necessary. When pus is obtained it may contain no amœbæ, but the absence of large numbers of polymorphonuclear leukocytes and the presence of much granular material will suggest that the origin is amœbic.

The diagnosis of amœbic hepatopulmonary abscess may be definitely made when the patient suddenly begins to expectorate quantities of reddish-brown anchovy-sauce sputum containing liver cells, hematoidin crystals, and amœbæ. The latter are always present, though sometimes a prolonged search is necessary to find them.

Prognosis.—There is no doubt of the gravity of the disease, and when well-advanced before proper treatment is instituted, the final outlook is often doubtful. The symptoms in the majority of cases yield to treatment in a short time and the patient may feel quite well. This may happen a number of times, and among this class of patients the mortality is always high. In untreated patients who are exposed to hardships, the death-rate is very great. Out of 78 collected cases (Harris) in the United States there were 30 deaths. In the Johns Hopkins series of 119, 28 terminated fatally; however, in both of these series it seems probable that many were well-advanced before treatment was instituted.

In the writer's series of 200 treated cases, which included all stages of the disease and from which accurate data were obtained, there have been 12 deaths and 4 are chronic invalids; the remainder have recovered. Tuttle reported 73 cases in the United States with 70 recoveries; and Deeks¹ has recently reported 282 cases in Panama treated by various methods with a mortality of 21.6 per cent. In children the prognosis is almost always good. Amberg and Musgrave each report 1 death. Adding together these series we have 44 cases in children with 2 deaths, a mortality of 4.5 per cent.

In the uncomplicated cases, those with acute onset, including the gangrenous form, usually have the gravest outlook. The writer cannot agree that a mild onset is no indication of a favorable course, for when treatment is instituted early these cases usually progress favorably.

In liver abscess the outlook is always very grave. Under careful treatment usually not more than one-third of the cases recover. In a collection of 1904 cases made by Solonoff² the mortality was 30 per cent. Davidson reported that of 522 admissions in the Army of India for the three years 1901 to 1903 with this complaint, no fewer than 286 of the patients died and a considerable number were invalided who doubtless increased the death roll. Fletcher reports 19 deaths out of 27 cases; 17 of these were operated upon but only 5 recovered. In the writer's clinical series of 200, abscess of the liver occurred in 12, 3 of whom recovered after operation. While the prognosis when hepatopulmonary abscess exists is usually very grave, some authorities regard the prognosis in cases in which the abscess has ruptured into the lung as fairly favorable.

¹ *Journal of the American Medical Association*, 1913, ix, 40.

² *British Medical Journal*, 1903, i, 262.

Rupture into the general peritoneal cavity and pericardium is practically always fatal.

Immunity.—While in many instances there seems to be a natural resistance to the disease, it would appear doubtful if there is any acquired immunity against it. The apparent natural resistance may depend upon the fact that the parasites are killed before reaching the large intestine, or that they do not find favorable conditions. The amœbæ, after the development of the disease, may disappear from the stools independently of treatment, but this may be brought about by unfavorable conditions in the intestine rather than by any acquired immunity. Sellards has been unable to show any amœbicidal action of the blood serum in cases of amœbic dysentery against amœbæ in the stools.

Treatment.—Prophylactic.—Since the disease is only acquired by the ingestion of certain species of entamœba in food or drink, it is a preventable one, and may be avoided even when the malady exists endemically. Drinking water is the most usual medium, and hence in a region where the disease is endemic it is advisable to sterilize this. Salads and uncooked fruits are sometimes a possible means of conveyance and should be avoided unless prepared with great care.

General, Dietetic, and Symptomatic.—Patients with acute onset or acute exacerbations of the disease should be confined to bed. In the most severe forms when very frequent bloody mucous stools are being passed, the diet should at first consist of nothing but rice or albumen water. Later milk may be added. Rest is most essential, and for this hypodermic injections of morphia sulphate (gr. $\frac{1}{4}$, gm. 0.016) may be given every three or four hours. Its use should be pushed if necessary. Local treatment in this stage is contra-indicated, but treatment with ipecac usually should be commenced. The essential point is to secure rest for the patient and for the acutely inflamed bowel. If this can be accomplished the condition usually improves. As the symptoms begin to abate, Dover's powder (gr. 10, gm. 0.6) may be substituted for the morphia. If the patient be seen before the symptoms are very acute a saline purge may be given, but if the severe symptoms have set in this is contra-indicated. In the mild attacks and those of very moderate severity it has become the custom in Manila not to confine the patient to the house but to allow him to be about and to enjoy a liberal diet. Many are better off when not confined to bed for the reason that they are likely to retain their strength better when up; but rest at home is usually advisable.

Where any intestinal irritation exists the diet should be restricted. Fresh milk, when obtainable, should be chiefly employed. It may be necessary to peptonize it, and this should be done if curds appear in the stools. If it is not well-borne, other liquid nourishment may be substituted. It is of course advisable to feed the patient frequently and in small quantities. As the symptoms improve, other liquids and soft food may be gradually added. Not until the stools appear perfectly normal should general diet be permitted.

Nausea and vomiting are frequently annoying and may result from treatment or be one of the results of the disease. The vomiting is very

rarely persistent or continued. The alkaline carbonated waters will sometimes give relief, and strychnine sulphate may be employed in tonic doses. Pepsin, hydrochloric acid, and pancreatin are rarely of benefit. In some, sodium bicarbonate with bismuth gives the best results.

The use of *bismuth* is not contra-indicated in the treatment of amœbic dysentery. Some writers have thought that it may interfere with the local treatment. This may be true where it is allowed to accumulate in the bowel. It occasionally is of service when diarrhœa persists, for by its use in one-dram doses every three or four hours constipation may be produced and a condition of the intestine brought about in which the amœbæ die out. Obviously one must not be led away with the idea that because the diarrhœa has stopped the lesions are healed and the parasites have disappeared. Repeated examination of the stools must be made to ascertain if the amœbæ have really died out. When bismuth is employed, a saline cathartic followed by a high rectal enema should be given at least once or twice a week.

In some instances an acute attack of diarrhœa has brought patients for treatment. They have been confined to bed for a few days, several doses of Dover's powder administered, and in some local treatment instituted. The parasites may never be found in the stools after the first week, though numerous in the first examination. The symptoms will subside during this time and a recurrence does not take place. In other cases with identical treatment the parasite may persist for weeks or months. The only explanation is that in one instance conditions in the intestine unfavorable to the life and propagation of the amœbæ are brought about, and in the other we fail to produce them. In the year 1910 Bowman and the writer treated 60 cases infected with amœbæ merely by rest in bed, diet, and an occasional dose of Rochelle salts. In 20 of these the amœbæ disappeared from the stools and the patients entirely recovered.

Abdominal *pain* may be very troublesome. It may be relieved by turpentine stupes and hot fomentations; or, if severe, opium may be administered. When ulcers exist in the rectum and there is much tenesmus, local treatment with argyrol or some other astringent or antiseptic substance may be applied through the speculum after the administration of a small enema containing cocaine or morphia. Enemas of starch and opium sometimes have a very soothing effect. If anemia is advanced some iron preparation is necessary; and when there is much lassitude and anorexia, a course of strychnine and alcohol in moderation is often of value. A change of climate is beneficial during convalescence, and patients who after a long time make no progress in the tropics are often improved by a bracing cool atmosphere.

The usual intestinal antiseptics by the mouth frequently have practically no effect upon the parasites in the large intestine, or generally over the course of the disease. Calomel in divided doses has many advocates. It may be employed with good results when the usual symptoms indicating its use appear; but apparently has no definite influence upon the parasites. When the patients have no stool except after an enema, or in cases with constipation, either small doses of calomel or a saline purge

should be administered at least once a week. The administration of quinine by the mouth on account of the effect it may have upon the amœbæ in the tissues has been advocated, but it cannot be given in sufficiently large doses owing to cinchonism.

Curative Treatment.—The results from *ippecacuanha* show that this drug must be considered the most valuable one in the treatment of this disease. Solutions of ipecac and particularly those of emetine in low dilutions are capable of destroying the parasites.

While in the author's experiments solutions of ipecac have not shown as great amœbicidal action as quinine sulphate against free living amœbæ in cultures, nevertheless in a very large percentage of the cases of amœbic dysentery the amœbæ disappear from the stools after the administration of ipecac and emetine in sufficient dosage. In some instances, even in the cases of moderate intensity as well as in severe ones, after thorough treatment with ipecac or emetine, the parasites and dysentery persist and the patients are not benefited. Relapses also not infrequently occur. A number of cases in the author's experience, which have resulted fatally, have been thoroughly treated with ipecac. Even Rogers, who was formerly most enthusiastic in regard to the ipecac treatment, but who now believes emetine to be superior, reports in one of his most recent articles¹ a dozen cases in a series of 30 which were treated with ipecac for from two to twenty days without favorable result; 8 of these died of amœbic dysentery. One of the cases was treated for twenty days and had received 1000 grains of ipecac but was not improved.

However, treatment with ipecac or with emetine should be tried in practically all cases. The patient should be placed in bed and no solid food given for six hours before and no liquids for three hours before the administration of the ipecac. A reliable preparation should be employed, perhaps best in five-grain (0.3 gm.) pills, freshly coated with salol or keratinized; from 40 to 60 grains (3 to 4 gm.) being administered twice a day for from two to three days. If the amœbæ fail to disappear and the symptoms continue, this treatment may be repeated, and, if the patient is able to stand it, it may be continued for several weeks. Immediately following the administration of the ipecac, the patient should lie flat upon his back and an ice-bag may be placed upon the epigastrium and upon the throat. This sometimes aids in preventing nausea. Manson prefers placing a mustard plaster upon the epigastrium for this purpose. Twenty drops of laudanum or a hypodermic injection of morphine sulphate may be given a short time before the ipecac.

More recently Rogers² has employed emetine hydrochloride or hydrobromide administered hypodermically or intravenously. The hydrobromide is not so soluble; the usual dose has been from gr. $\frac{1}{3}$ to $\frac{1}{2}$ (0.022 to 0.032 gm.) three times a day for two or three days; the maximum dose was one grain. No depression or vomiting occurred after these doses. As much as one grain (0.065 gm.) in 5 cc. of saline solution has been injected intravenously without any apparent depression following.

¹ *Indian Medical Gazette*, November, 1912.

² *Brit. Med. Jour.*, 1912, i, 1424, and ii, 405; and *Indian Med. Gaz.*, 1912, ii, 421.

Of 26 cases treated subcutaneously with emetine, 24 were cured and 4 died, 2 of intercurrent disease. The advantages of employing the emetine hypodermically are stated to be that this method practically does away with nausea.

In those cases which do not yield to ipecac, local treatment by rectal injections and irrigations is often efficacious. After employing many substances, the writer concluded that quinine solutions give the best results. The fluid should be allowed to enter slowly and the hips should be elevated. The solution may be 1 to 5000 or 1 to 1000 to begin with, and after a few days should be increased to 1 to 500 and used continuously at this strength. The amount injected should usually be about two liters; some patients will be able to take more and some less. The enema should be retained if possible fifteen minutes, and at least five minutes. Difficulty may be encountered in giving these large injections, and in passing the rectal tube its whole length. The attending physician should, for a few days, either administer the enemas himself or have a trained assistant do so. The writer has never seen an accident from this treatment. It is sometimes necessary when the rectum is very irritable to introduce a cocaine suppository first; or the irrigations may be suspended for a day or two.

One or two enemas daily are usually sufficient. In certain cases in robust individuals as many as three may be employed. A greater number than this will probably always do more harm than good. It is probable that the mere flushing out and cleaning of the colon plays an important rôle, and many recover when saline solutions or ordinary water enemas are employed. It is obvious that this washing out must not be performed too often or the general condition of the patient may suffer, and the mucosa itself be injured and healing delayed. There are a number of cases in which the parasites persist even after all symptoms have disappeared and we are not able to rid the patient of them by any known means. In other instances the parasites appear to persist chiefly owing to their burrowing in the submucosa where we are not able to reach them by treatment. In those cases in which the lesions have healed and the parasites still persist, the time to discontinue treatment is important. If it is decided to interrupt the treatment and local treatment is being pursued, the enemas should be gradually reduced to one or two a week before their complete withdrawal, and the stools carefully watched for blood cells or other evidences of intestinal disturbance. The prolonged local treatment for several months usually brings about a catarrhal condition of the large intestine which may exist for a long time or remain permanently.

In patients with suspected lesions in the cecum which do not yield to either oral, or local treatment by the rectum, colostomy has been recommended, or the appendix has been drawn out and amputated and the irrigations given directly through the cecum.

Treatment of the Complications.—*Abscess of the liver* should be opened and freely drained as soon as the diagnosis is made, unless it has already perforated into the lung and is being freely discharged through a bronchus. If the abscess is opened it should be frequently irrigated with quinine

solution. Manson and Cantlie advocate drainage by means of a trocar and cannula and the establishment of a siphon drainage. Rogers points to the danger of postoperative infection in India and also recommends aspiration of the pus and the injection of quinine solution or of emetine (1 grain to 2 ounces of water) by means of a special trocar with a flexible silver sheath. Charles, however, prefers the open operation, preceded by aspiration, on the ground that drainage by these methods is not thorough.¹ If the abscess is not found or no operation is performed medical treatment may be instituted. Rogers² believes that liver abscess may be frequently prevented, and even arrested, provided that ipecac is given in the presuppurative stage of the infection in doses of 30 to 60 grains (2 to 4 gm.), the dose being continued for from two to three weeks. Chauffard³ has reported the treatment of a liver abscess which had opened into the bronchial tubes. When treatment with emetine was begun, the fistula had persisted for five months. After six injections, each of 0.4 gram, of emetine hydrochloride had been given the abscess and fistula healed. *Perforation* of the bowel demands surgical aid if the condition of the patient warrants it, but there is little hope of recovery. Morphia should be administered for the pain. *Local peritonitis* without perforation requires rest and the application to the abdomen of ice or hot fomentations, with opiates by the mouth. For serious *hemorrhage*, morphia should be given and ice applied locally to the abdomen. Ice-cold or hot enemas containing tannin, silver nitrate, or calcium chloride, may be tried in extreme cases. Stimulants and subcutaneous or intravenous injections of salt solution should be employed when their use is indicated. Adrenalin may also be tried. For the treatment of *brain abscess* extensive trephining is necessary and the abscess should be sought for with a channeled sound and not with an aspiration needle, since the pus is viscid and flows reluctantly.

¹ For a detailed description of the operation see *Brit. Med. Jour.*, 1908, ii, 1242.

² *Phil. Jour. Science*, 1908, iii, p. 285, and *Brit. Med. Jour.*, 1908, ii, p. 1246.

³ *Bull. de l'Acad. de Méd.*, Paris, February 25, 1913, lxxvii, 109.

CHAPTER II

THE MALARIAL FEVERS

By CHARLES F. CRAIG, M.D.

Definition.—By the term malarial fevers we mean a group of specific infectious fevers due to infection of the red blood corpuscles of man by closely related animal parasites belonging to the *Sporozoa*, genus *Plasmodium*.¹ These fevers occur epidemically or endemically and are accompanied by a symptom complex which is more or less characteristic of each variety. Periodicity is one of the most marked clinical phenomena and is due to the growth of the plasmodia. All malarial infections are transmitted by mosquitoes of the family *Anophelina*, and so far as is known at the present time, this is the only means of transmission.

Geographical Distribution. There is no infectious disease which can compare with the malarial fevers in the extent of its geographical distribution. In the eastern hemisphere malarial infections do not occur above 62° N. Latitude, while in the western hemisphere they are very rarely found above 45° N. Latitude. They are most common and severe in low-lying coast regions, mountainous countries being comparatively exempt. The deltas of large rivers, especially the rivers of tropical countries, are hot-beds of malarial disease, and this is also true of all bodies of water situated in such localities. As the equator is approached we meet less often with the benign forms of malarial infection, the prevailing types being the severe and often fatal estivo-autumnal infections. The most important malarial localities are the following:

North America.—In North America, malaria occurs rarely above the forty-fifth parallel, but is often frequent and fatal in the Southern States and in the West Indies, especially in Cuba, as well as in Central America. In the New England and Middle Atlantic States the benign forms are present, but are comparatively rare. The severe forms prevail along the low regions of the southern coast line, and especially in the swampy regions of the Gulf States. These infections are common and severe along the Mississippi River and its southern branches, and they are present in many of the Western States, especially in the river valleys of California, where severe and fatal estivo-autumnal infections are not uncommon. The regions about the Great Lakes are almost free from malaria except

¹The malarial parasites belong to the *Sporozoa*, sub-order *Hemosporidia*, genus *Plasmodium*. The name *Plasmodium* was first given to these organisms by Marchiafava and Celli, and is very unfortunate from a biological standpoint. Grassi has suggested the name *Hamamæba* for the parasites, and this is a preferable term to *Plasmodium*, but the latter term will have to be retained because of the law of priority. The same objection may be raised to the name "malaria," which was derived from the Italian, meaning bad air. In the light of our present knowledge the name is erroneous, but will have to be retained as it has become so firmly established.

in certain localities about Lake Michigan. Canada is the only country in North America which appears to be almost entirely free from malaria.

South America.—In South America, severe types of the disease are common, especially along the coast regions of Columbia, Venezuela, Guiana, Brazil, Ecuador, Peru, and Chile. The whole Atlantic coast line of Central America is severely infected with estivo-autumnal malaria, and in this region the most pernicious forms are common.

Europe.—Malarial fevers occur but rarely in England, Germany, and France. In Germany they occur along the coast of the Baltic, especially in Prussia, and they are not uncommon in the swamps of Hanover and Westphalia, and along the Rhine; in France these infections occur along the Loire and Rhone on the west coast; in Spain the valleys of the Tago and Guadalquivir are infected, and pernicious forms occur in all the countries bordering upon the Mediterranean; in Greece, Crete, Italy, Sicily, and Turkey, malaria is endemic; in Italy, especially, occur the most malignant forms in the regions around the Roman Campagna and the Pontine marshes, as well as in the valley of the Po; in Russia malarial infections are present in the valleys of the Volga, Dniester, Dnieper, and also in the regions bordering on the Black and Caspian Seas.

Asia.—India, Ceylon, portions of China and Arabia, and the islands of the Malay Archipelago are infected with the malarial fevers. This is also true of Asia Minor and the valleys of almost all the great rivers, such as the Indus and Ganges. In Japan the benign infections are common, and even upon the lofty table lands near the Himalayas malarial infections are often met with. The Philippine Islands, until very recently considered as comparatively free from malarial disease, have been proved to be badly infected, a large percentage of our soldiers returning from there showing infection with the tertian and estivo-autumnal parasites.

Africa.—In Africa are some of the most dangerous lurking places of malarial infections, the worst areas being those along the west coast and the Senegal, Congo, and Niger Rivers, as well as the regions around the great lakes and the jungles and lake shores of Abyssinia. Madagascar, Reunion, and Mauritius Islands present the pernicious varieties of the disease. Around Delagoa Bay and along the east coast of Africa, estivo-autumnal fever is prevalent. Lower Egypt, the Soudan, the Nile delta, Tripoli, Tunis, and Algeria, all harbor these infections.

While these are the most important localities in which malarial infections are endemic, there are numerous districts in which a few sporadic cases occur, but which may at any time become endemic foci, provided certain species of mosquitoes belonging to the *Anophelinæ* are present, together with individuals harboring the parasites.

Etiology.—The history of the discovery of the parasites concerned in the etiology of the malarial fevers furnishes one of the most interesting chapters in the annals of medicine. The bacterial origin of the malarial infections was believed in for a considerable period of time, until in 1880 Laveran¹ described certain parasites occurring in the blood

¹ *Bull. de l'Acad. de Méd.*, Paris, 1880, xciii, 644-658.

which he considered as the cause of the disease. His observations were soon confirmed by Richard, Marchiafava and Celli, Golgi, Councilman, Abbot, Sternberg, Osler, and Dock. In his original communication Laveran described three forms of the parasite. The first consisted of oval or crescentic bodies with hyaline protoplasm containing pigment, arranged either in clumps or in a wreath-like arrangement. This form was undoubtedly the crescentic form of the parasite causing estivo-autumnal malaria. The second form described consisted of small hyaline bodies containing pigment; and from these bodies there arose occasionally long, thin, hyaline filaments which possessed the property of motion. This form was undoubtedly the flagellated form of the estivo-autumnal parasite. The third form described by him consisted of spherical, slightly granular bodies, with motionless pigment, which were evidently degenerative forms of the two foregoing classes. Richard¹ later described the intracorpuseular hyaline parasites and the segmenting bodies. In 1885 Marchiafava and Celli² described carefully the hyaline and intercorpuseular parasites, and proposed the term *Plasmodium malariae* for the organism. Biologically, this term is very inaccurate and should be abandoned, as the parasites belong to the sporozoa, but the name is so firmly fixed that it will probably have to be retained. In the same year, Golgi³ proved that quartan fever depended upon a specific form of the malarial parasite, and shortly afterward he also differentiated and described the parasite causing tertian fever. To him we also owe the discovery that the malarial paroxysm always coincides with the segmentation or sporulation of a group of parasites. In 1885 Golgi also called attention to the probably distinct type of the crescentic and ovoid forms of the organism, and Councilman first called attention to the diagnostic value of the various forms which are observed in the blood. In 1889 Golgi added to his studies concerning the development of the crescents, showing that they arose from the small, cellular rings, and that this parasite was associated with fever of a remittent character. To him belongs the credit, therefore, of first clearly differentiating the estivo-autumnal parasite.

Classification.—The classification of the parasites causing malaria has occupied the attention of zoölogists for many years, and a great many different opinions have been advanced regarding their exact position. At the present time it is conceded by all that they belong to the *Sporozoa*, and the following classification adopted at present by nearly all authorities is the one followed in this contribution. All the plasmodia of man are placed in the suborder *Hæmosporidia*, and are divided into the following species: *Plasmodium vivax* (tertian parasite), *Plasmodium malariae* (quartan parasite), and *Plasmodium falciparum* (estivo-autumnal parasite). The Italian authorities, together with nearly every investigator who has studied malaria in the tropics, have made a subdivision of the estivo-autumnal parasite into two varieties, the quotidian and tertian. A large amount of labor has been expended in

¹ *Gaz. Méd. de Par.*, 1882, xx, p. 252.

² *Fortschritte der Med.*, 1885, iii, 787.

³ *Arch. per le scienz Méd.*, 1886, x, 109-135.

EXPLANATION OF PLATE V.

PLASMODIUM VIVAX (TERTIAN PLASMODIUM).

Stained with Wright's modification of the Romanowsky method.

FIG. 1.—Young schizont, the so-called "ring-form."

FIG. 2.—Slightly older schizont.

FIG. 3.—Double infection of red corpuscle with schizonts. Note the presence of Schuffner's dots.

FIGS. 4, 5, and 6.—Young pigmented forms of the tertian schizont.

FIGS. 7, 8, 9, and 10.—Tertian schizonts showing the division of the chromatin of the nucleus, enlargement of the infected erythrocytes, and increase in the amount of pigment.

FIG. 11.—Pre-sporulating tertian schizont.

FIG. 12.—Sporulating tertian schizont.

FIG. 13.—Free spores, or merozoites, of *Plasmodium vivax*.

FIG. 14.—Microgamete of *Plasmodium vivax*.

PLASMODIUM MALARIÆ (QUARTAN PLASMODIUM).

Stained with Wright's modification.

FIG. 1.—Young schizont, or so-called "ring-form."

FIG. 2.—Double infection of erythrocyte, with quartan schizonts.

FIGS. 3 and 4.—Young pigmented schizonts.

FIGS. 5 and 6.—Half-grown forms of *Plasmodium malariae*, showing the division of the chromatin.

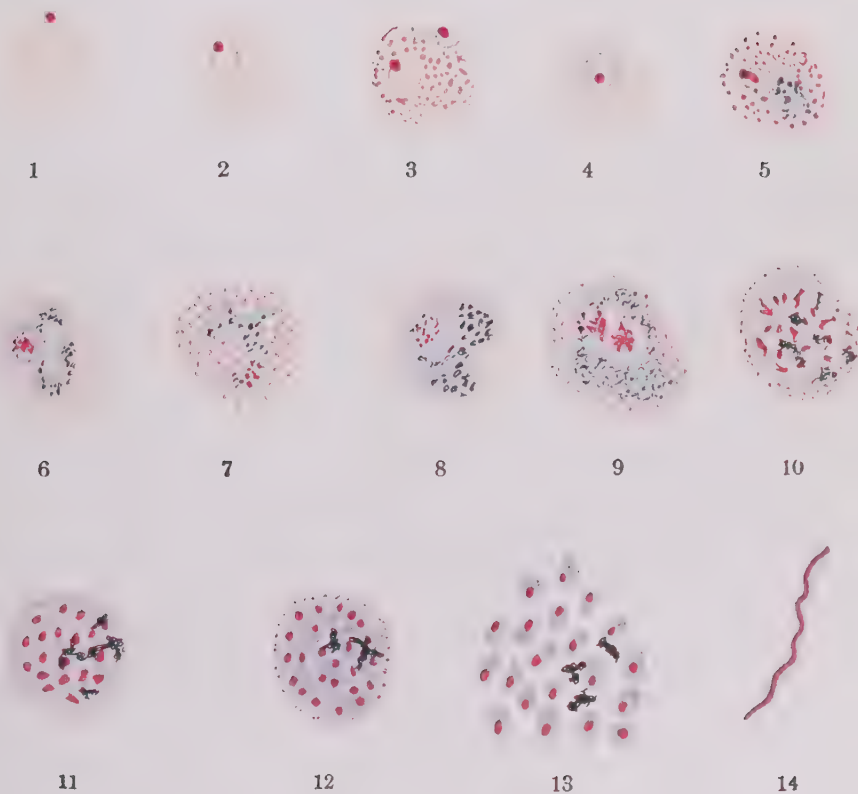
FIG. 7.—Pre-sporulating schizont of *Plasmodium malariae*.

FIG. 8.—Sporulating schizont of *Plasmodium malariae*. (Note smaller number of merozoites, and lack of enlargement of the erythrocyte, as in the tertian plasmodium.)

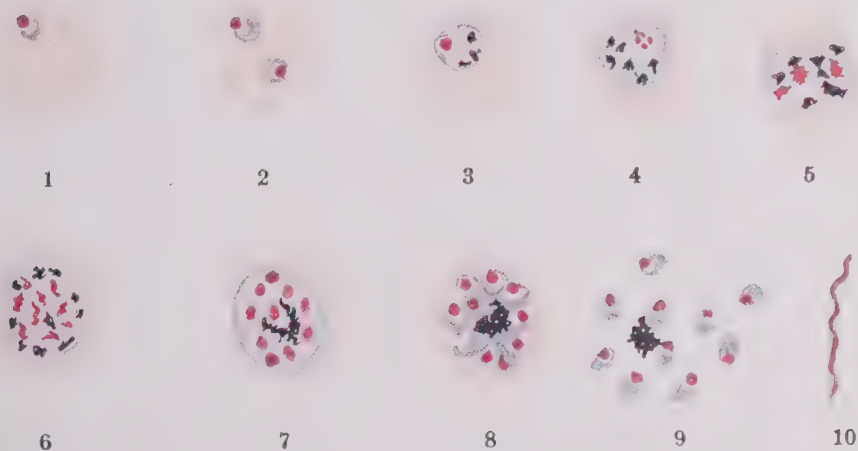
FIG. 9.—Free spores or merozoites of *Plasmodium malariae*.

FIG. 10.—Microgamete of *Plasmodium malariae*.

PLATE V



Plasmodium Vivax (Tertian Plasmodium).



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Plasmodium Malariae (Quartan Plasmodium).

EXPLANATION OF PLATE VI.

PLASMODIUM FALCIPARUM (TERTIAN ESTIVO-AUTUMNAL PLASMODIUM).

Stained by Wright's modification of the Romanowsky method.

- FIG. 1.—Sporozoite, just attached to an erythrocyte.
FIG. 2.—Young schizont, the so-called "ring-form."
FIG. 3.—Double infection of erythrocyte by two young schizonts, or "ring-forms."
FIG. 4.—Fully developed "ring-form" of the tertian estivo-autumnal plasmodium.
FIGS. 5, 6, 7, and 8.—Developing schizonts of *Plasmodium falciparum*, showing increase in size, development of pigment, and division of the nuclear chromatin.
FIG. 9.—Pre-sporulating stage of *Plasmodium falciparum*.
FIG. 10.—Sporulating schizont of *Plasmodium falciparum*. Note absence of Schuffner's "dots" in this infection.
FIG. 11.—Macrogametocyte, or female gamete of *Plasmodium falciparum*. The so-called crescent form.
FIG. 12.—Microgametocyte, or male gamete of *Plasmodium falciparum*.

PLASMODIUM FALCIPARUM QUOTIDIANUM (QUOTIDIAN ESTIVO-AUTUMNAL PLASMODIUM).

Stained by Wright's modification.

- FIG. 1.—Sporozoite just attached to the erythrocyte.
FIG. 2.—Young schizont, or "ring-form." Note very minute size.
FIG. 3.—Triple infection of the erythrocyte, with "ring-forms" of the quotidian estivo-autumnal plasmodium.
FIG. 4.—Fully developed "ring-form" of the quotidian species.
FIGS. 5, 6, 7, and 8.—Various stages in the growth of *Plasmodium falciparum* quotidianum, showing increase in size, development of pigment, and division of the nuclear chromatin.
FIG. 9.—Pre-sporulating schizont of the quotidian estivo-autumnal plasmodium.
FIG. 10.—Sporulating schizont of *Plasmodium falciparum* quotidianum. Note minute size of the spores, or merozoites, and the large amount of erythrocyte still preserved. In both estivo-autumnal infections note the absence of enlargement of the erythrocyte, and of Schuffner's "dots," or granules.
FIGS. 11 and 12.—Female and male crescents of this species. Note small size.

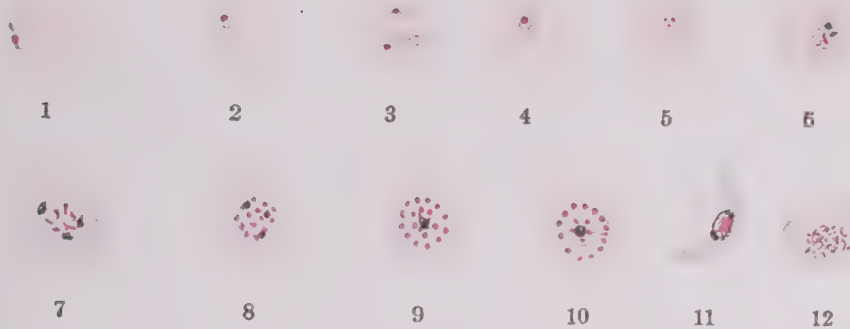
GAMETES OF TERTIAN AND QUARTAN PLASMODIA.

- FIG. 1.—Young microgametocyte of *Plasmodium vivax*.
FIG. 2.—Well-developed microgametocyte of *Plasmodium vivax*.
FIG. 3.—Young macrogametocyte of *Plasmodium vivax*.
FIG. 4.—Fully developed macrogametocyte of *Plasmodium vivax*.
FIG. 5.—Flagellated microgametocyte of *Plasmodium*, the flagella constituting the microgametes.
FIG. 6.—Young macrogametocyte of *Plasmodium malariae*.
FIG. 7.—Developed macrogametocyte of *Plasmodium malariae*.
FIG. 8.—Young microgametocyte of *Plasmodium malariae*.
FIG. 9.—Fully developed microgametocyte of *Plasmodium malariae*.
FIG. 10.—Flagellated microgametocyte of *Plasmodium malariae*, the flagella being the microgametes. Note the lighter staining of the male, or microgametocytes, and the different arrangement of the nuclear chromatin.

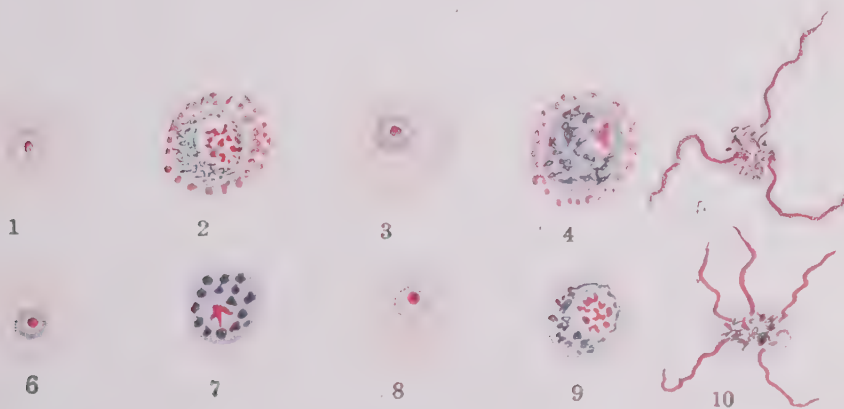
PLATE VI



Plasmodium Falciparum (Tertian Estivo-autumnal Plasmodium).



Plasmodium Falciparum Quotidianum (Quotidian Estivo-autumnal Plasmodium).

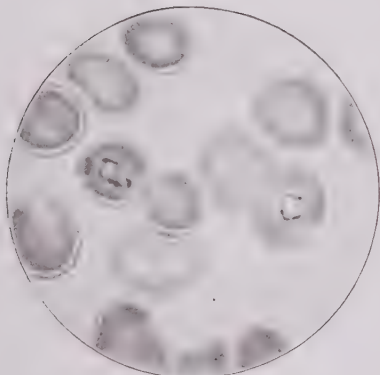


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Gametes of Tertian and Quartan Plasmodia.

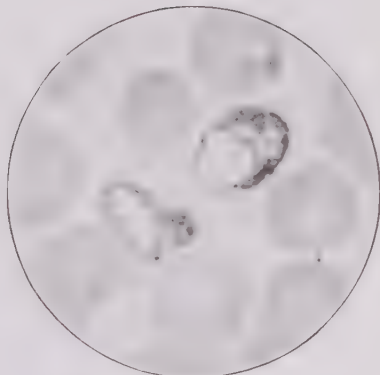
PLATE VII

Fig. 1



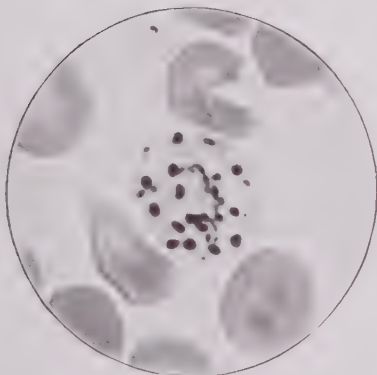
Plasmodium vivax (tertian). Ring form.
× 1200.

Fig. 2



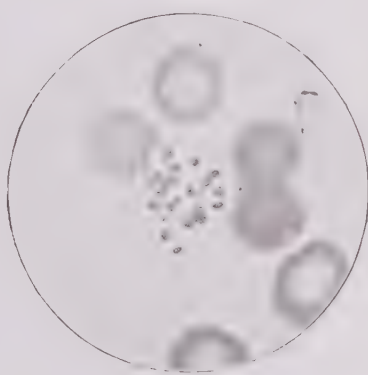
Plasmodium vivax (tertian). Half-grown
pigmented form. × 1500.

Fig. 3



Plasmodium vivax (tertian). Sporulating
form. × 1800.

Fig. 4



Plasmodium vivax (tertian). Free spores.
× 1200.

differentiating these varieties of the estivo-autumnal parasite, and it is undoubtedly true that they can be differentiated when the material is available for study. The writer is satisfied that the quotidian and tertian estivo-autumnal parasites can be as easily differentiated as the tertian and quartan. For the parasite causing the quotidian type of estivo-autumnal fever I have proposed the name *Plasmodium falciparum quotidianum*, considering it a subspecies of *Plasmodium falciparum*.

The malarial plasmodia are found in man within the red-blood corpuscles and are essentially parasites living upon and within these cells. In this situation they destroy the red corpuscles and produce the well-known anemia peculiar to malarial fever, together with the pigmentation, or melanemia, which is due to the destruction of the hemoglobin of the red cell. In describing these parasites two life cycles must be considered: first, the human cycle, *schizogony*, or asexual cycle, occurring within the infected individual, and second, the mosquito cycle, *sporogony*, or sexual cycle, occurring within the infected mosquito. These fevers are not infectious from patient to patient except through the intermediation of certain mosquitoes.

Plasmodium Vivax—(The Tertian Parasite)—(Schizogony, Human Cycle).
—The tertian parasite, or *Plasmodium vivax*, appears first within the red cell in schizogony as a small actively amœboid hyaline body, the *schizont*, of various shapes, the difference in outline being due to the rapidity and extent of the amœboid movement. At first the outline of the organism is very indistinct and careful examination is needed to distinguish it. As the organism grows older and becomes pigmented it is much more easily distinguished. The hyaline stage is quickly followed by the appearance of a few minute granules of reddish-brown pigment situated within it and showing active movement. This movement is due to protoplasmic currents within the parasite. In the beginning, occupying but a minute portion of the red cell, as it continues to grow, the parasite encroaches more and more upon the infected corpuscle, until when full-grown it fills the entire cell. The growth of the parasite is gradual, covering forty-eight hours. The full-grown parasites have a rather distinct outline and the red cells containing them are greatly swollen, sometimes to almost double the size of the normal red-blood corpuscle. Toward the end of thirty-six hours the organism has approached nearly to its full growth, only a narrow rim of the red cell showing around it. Amœboid motion has become almost entirely lost, the parasite being circular in shape, well-defined, the pigment more or less motile and much increased in quantity, still, however, finely granular in appearance and reddish brown in color. At the end of forty-eight hours segmentation takes place, the pigment becomes collected at the centre or to one side of the organism in the form of a compact clump and fine radial divisions are noticed branching from the centre toward the periphery of the organism, thus dividing the parasite into small ovoid segments. As a rule, there are two rows of these segments, one row surrounding the centre, and another surrounding the first row, but very often the segments are irregularly arranged, and they are always devoid of pigment. They vary in number from twelve to twenty-four, the average being about

sixteen, and are known as *merozoites*. At the time that segmentation occurs the infected red cell has apparently disappeared, being entirely destroyed by the invading parasite. The destruction of the red cell, which is complete at the time of segmentation, liberates the segments, or *merozoites*, which are again capable of infecting new corpuscles, and thus the human life cycle or schizogony continues. The pigment, which is not present at the beginning of the life cycle in the red-blood corpuscle, gradually increases as the degeneration of the red cell continues, being derived from the destroyed hemoglobin of the cell. In all the pigmented forms of the tertian parasite the pigment is generally motile.

In examining blood from tertian cases it will be noticed that a certain proportion of the full-grown parasites do not segment, and it is these which are intended to commence the life cycle of the organism in the mosquito, which will be described later.

Plasmodium Malariae—(The Quartan Parasite)—(Schizogony, Human Cycle).—Like the tertian parasite, the organism causing quartan malarial infection appears at first within the red corpuscle as a small actively amœboid hyaline body without pigment, the *schizont*. It will be noticed that the amœboid motion is less marked than in the case of the tertian organism. The quartan parasite rapidly becomes pigmented, the pigment being collected in larger granules than is the case in the tertian parasite, being less motile and arranged around the periphery of the organism, whereas in the tertian parasite the pigment is distributed throughout the protoplasm. The outline of the organism is also much more distinct than is the case in the tertian parasite during all stages of its growth. Instead of the swollen decolorized red cell seen in the tertian infection, the infected corpuscle in quartan fever is normal in size and often slightly below normal, and darker green in color, instead of pale. This difference serves at once to distinguish the two varieties upon microscopic examination of the blood. The parasite slowly increases in size, and in doing so becomes less amœboid. The pigment increases in quantity and becomes collected at the extreme periphery of the organism and is absolutely immotile. The granules of pigment are considerably larger than in the tertian parasite, darker in color, and at no stage of the growth of the organism do they collect in small clumps throughout the protoplasm, as is common in the tertian form. As growth increases the parasite tends more and more to fill the infected red cell, and when full-grown—that is, at the end of seventy-two hours, it almost fills the cell, a small greenish rim of hemoglobin still being visible around the organism. At this stage of its growth the parasite is very distinctly outlined and is much more refractive than is the tertian species; the pigment is absolutely motionless and collected around the periphery; the shape is circular and amœboid motion has entirely ceased. At the end of seventy-two hours segmentation occurs, the pigment becoming collected at the centre or in a star-like arrangement distributed from the centre. Radial striations appear dividing the organism into from eight to twelve segments, or *merozoites*. The segments are generally arranged in a perfectly symmetrical manner around the central pigment, giving the so-called daisy or “Marguerite” appearance

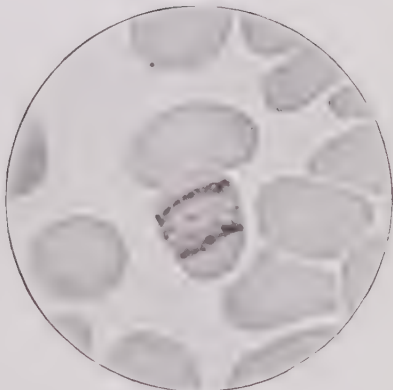
PLATE VIII

Fig. 1



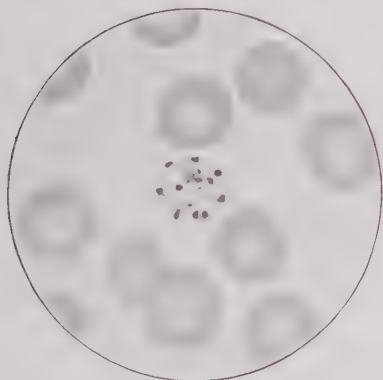
Plasmodium malariae (quartan). Ring forms. $\times 1500$.

Fig. 2



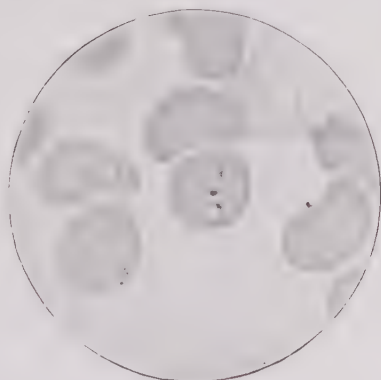
Plasmodium malariae (quartan). Half-grown "band" form. $\times 1800$.

Fig. 3



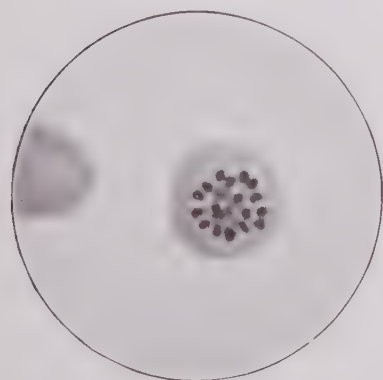
Plasmodium malariae (quartan). Sporulating form. $\times 1200$.

Fig. 4



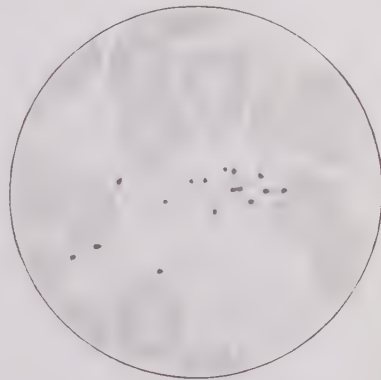
Plasmodium falciparum (tertian estivo-autumnal). Ring form. $\times 1500$.

Fig. 5



Plasmodium falciparum (tertian estivo-autumnal). Sporulating form. $\times 1800$.

Fig. 6



Plasmodium falciparum (tertian estivo-autumnal). Free spores. $\times 1200$.

to the parasite at this stage. When segmentation is complete, each merozoite becomes free in the blood plasma and, in the human life cycle, again invades the red corpuscles, undergoing the changes which have been described. As in the tertian form, certain parasites do not undergo segmentation, and these are the ones intended to carry on the life cycle in the mosquito.

Plasmodium Falciparum—(Estivo-autumnal Parasite)—**Tertian Form (Schizogony, Human Cycle)**.—As has been stated, the writer believes with Marchiafava and Bignami that there are two distinct varieties of the estivo-autumnal parasite, the tertian and quotidian. These are distinguishable microscopically and the symptoms produced by them are characteristic and easily differentiated clinically. In previous contributions¹ the differential points between these two varieties of the estivo-autumnal parasite and also the clinical phenomena which are produced by them have been described.

The tertian estivo-autumnal parasite appears first within the infected red cell as a round hyaline ring or disk. The infected corpuscle is greenish in color, smaller than the normal corpuscles surrounding it and generally crenated. The young parasites are considerably larger than the quotidian parasite, occupying from one-fourth to one-third of the total area of the infected cell. The ring forms are irregular in outline, one portion of the ring being larger than the rest, giving it the so-called "signet-ring" appearance. The organism is very highly refractive and sharply outlined, appearing as though it had been cut into the corpuscle with a punch. Amœboid motion is present, although it is less rapid than in the quotidian form, and only very rarely is more than a single parasite seen within one corpuscle. In the course of from twenty to twenty-four hours the hyaline forms become pigmented, the pigment occurring in the form of very fine, reddish-brown granules somewhat resembling those found in the tertian parasite. The pigment is in larger amount than in the quotidian parasite and is generally motile. As growth increases amœboid motion becomes lost, and this is also true of the peculiar ring-shape, which is so characteristic of this form of the parasite. At the time of segmentation, which occurs in forty-eight hours, the organism occupies about one-half of the infected red cell. The pigment is collected at the centre and radial striations start from this point and divide the parasite into ten or fifteen segments, or *merozoites*. In some instances as high as twenty-four *merozoites* have been counted. Segmentation occurs within the red-blood corpuscles, but its situation is not so easy to distinguish in this form as in the quotidian. The segmenting forms occur but seldom in the peripheral blood, although they are very numerous in certain cases in blood collected from the spleen. The young segments are liberated in the blood plasma and again infect the red cell; thus the human cycle is repeated.

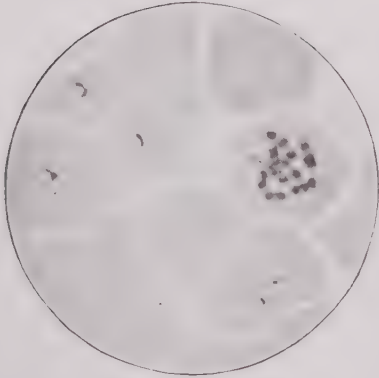
¹ *The Philadelphia Medical Journal*, April 7, 1900; also, *Journal of the American Medical Association*, November 3, 1900; *The Estivo-Autumnal (Remittent) Malarial Fevers*, Wm. Wood & Co., 1901; *International Clinics*, vol. iii, 13th series, October, 1903; *The Malarial Fevers, Hemoglobinuric Fever, and the Blood Protozoa of Man*, Wm. Wood & Co., 1909.

Plasmodium Falciparum Quotidianum—(Estivo-autumnal Parasite)—**Quotidian Form**—(Schizogony, Human Cycle).—The *quotidian* parasite appears at first in the infected red cell as a very minute ring-shaped or round hyaline body, the *schizont*, which upon close inspection shows very active amoeboid motion. The outline of the organism at first is indistinct, but gradually becomes more distinct and when full-grown it is very clear-cut and refractive. The round forms are perfectly hyaline in appearance but the ring form, which is most common, consists of a narrow hyaline body enclosing a small area which shows the normal greenish-yellow color of the infected corpuscle. This appearance is considered by most authorities to be due to the fact that the centre of the parasite is much thinner than the periphery, thus allowing the normal color of the corpuscle to show through. Careful observation of these ring forms, however, will show that they often become perfectly hyaline and in so doing the protoplasm of the organism flows in from the edge of the ring, thus tending to prove that no protoplasm existed in this greenish-colored area. The amoeboid motion is very active, but the organism has to be carefully watched in order to distinguish it. The infected red corpuscle is generally smaller in size than the normal corpuscle and darker green in color. It is very apt to be crenated. In many instances double or triple infections of the corpuscle may be observed. In the peripheral blood the hyaline, round or ring-shaped organisms are those which are most commonly observed, although a certain number of pigmented forms are not uncommon. The pigmentation is never as marked as in the tertian or quartan parasite, the pigment consisting of a small, solid block, almost black in color, situated at some portion of the edge of the parasite or at the centre; it is never motile. Very rarely the pigment consists of fine granules, but these granules never number more than three or four. The segmenting forms are but very seldom observed in the peripheral blood, although blood from the spleen taken at the proper time in well-marked cases presents numerous parasites undergoing this process. Segmentation occurs at the end of twenty-four hours. Just before segmentation the parasite occupies about one-fourth of the red-blood corpuscle, thus distinguishing it from the quartan and tertian varieties which fill the corpuscle. The pigment does not show any decided increase in amount and is absolutely immotile. At the time of segmentation this pigment becomes collected at the centre of the parasite and radial striations can be detected, starting from the centre and dividing it into from sixteen to eighteen very minute round or oval segments, or *merozoites*. While in the tertian and quartan forms it is often impossible to distinguish the remains of the red corpuscle when segmentation occurs, in this variety it can be plainly seen that segmentation occurs within the infected red cell. The merozoites are liberated by the entire destruction of the red corpuscle; each merozoite is capable of again infecting the red cell and the human cycle is thus repeated.

In this variety, as well as in the tertian form, peculiar bodies occur which are developed within the red blood corpuscle, but which do not undergo segmentation. These are the so-called crescents, which are so

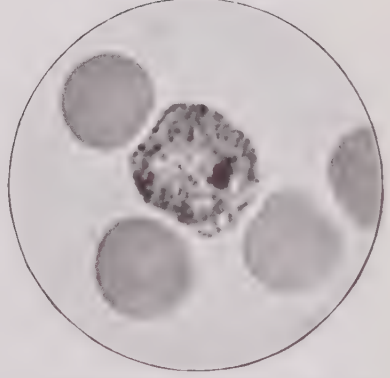
PLATE IX

Fig. 1



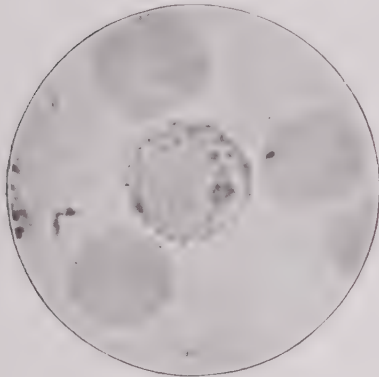
Plasmodium falciparum (quotidian). Ring form and sporulating form. $\times 2000$.

Fig. 2



Macrogamete of *Plasmodium vivax*. Full-grown female gamete or macrogamete. $\times 1800$.

Fig. 3



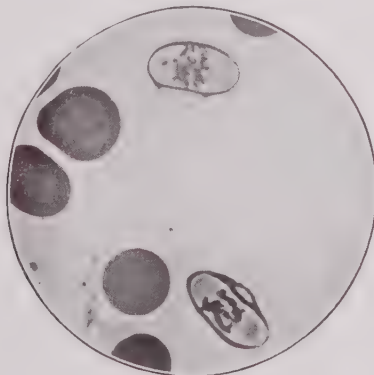
Microgametocyte of *Plasmodium vivax*. Full-grown male gamete or microgametocyte. $\times 1800$.

Fig. 4



Macrogametocyte of *Plasmodium falciparum*. Female crescent of estivo-autumnal parasite. $\times 1200$.

Fig. 5



Microgametocyte of *Plasmodium falciparum*. Male crescent of estivo-autumnal parasite. $\times 1200$.

characteristic of estivo-autumnal infections, and which will be described in considering the mosquito cycle of this parasite.

So far we have considered the human cycle of the malarial plasmodia, which consists, briefly, in the infection of the red-blood corpuscles by the merozoites which are derived from the segmenting bodies. The mosquito cycle, which is more complex, will now be considered.

Development of the Malarial Plasmodia within the Mosquito (Sporogony, Sexual or Mosquito Cycle).—As has been mentioned, in tertian and quartan infections, certain organisms occur which do not undergo segmentation. This is also true of the estivo-autumnal infections, in which a peculiar body known as the crescent appears, intended to continue the life cycle of the parasite within the mosquito.

Tertian and Quartan Forms.—In tertian and quartan infections, in blood which has been removed from the body for some time, peculiar bodies occur known as flagellated organisms. These bodies are of two kinds, which the writer designated in an early contribution¹ as active and passive flagellated organisms. These forms are now known to be sexual in nature, the active flagellated body being the male, the passive the female parasite. The active flagellated organism, or the *microgametocyte*, is spherical in shape and filled with actively motile pigment. This pigment is in the form of small granules which are distributed throughout the protoplasm of the organism. It will be noticed that in such round bodies the pigment becomes more and more active, until finally three or more serpentine prolongations of the protoplasm appear at the circumference of the organism. These prolongations are from three to four times the diameter of the parasite, are possessed of a very active lashing movement, and are known as flagella, or *microgametes*. With this form of the organism round bodies occur in which the pigment is collected in larger clumps and generally arranged around the circumference in the form of a perfect ring, while there is no evidence of motility. These are the passive flagellated organisms, or *macrogametocytes*, and never present the process of flagellation as seen in the *microgametocyte*, or active body. The flagella from the *microgametocyte* eventually become free in the blood plasma and sometimes can be seen attached to the bodies which have just been described, *i. e.*, the *macrogametocytes*. This process, however, takes place in nature in the middle intestine of the mosquito. A distinct difference has been demonstrated in the structure of the female *macrogametocytes* and the male *microgametocytes*. In the *macrogametocyte* the nucleus is of good size and situated at one side of the centre of the organism, containing little chromatin. In the *microgametocyte* the nucleus is always situated at the centre of the organism and contains a large amount of chromatin. When the flagella, or *microgametes*, develop from the *microgametocyte*, it has been demonstrated that the chromatin passes into them and forms an essential portion of their structure. Prior to the fertilization of the *macrogametocyte* by a flagellum or *microgamete* certain nuclear changes occur in the former and when completed the *macrogametocyte* is called a *macrogamete*.

¹ *New York Medical Journal*, December 23, 1899.

Estivo-autumnal Infections.—In the blood in these infections peculiar forms of the parasite occur known as *crescents*. These are developed within the red-blood corpuscle and are typically crescentic in shape. They are very refractive, having a more or less granular protoplasm, and contain within them, generally at the centre, but sometimes at one or the other pole, a clump of pigment arranged in the form of slender rods or minute dots. In the very young crescents the pigment is distributed throughout the protoplasm, but as the crescent matures it collects at the centre or at one end. The border of the crescent is sharply cut and is represented by a single or double line, having a peculiar greenish color. In most crescents, when full-grown, careful examination will show a dim line upon the concave side of the organism, which has a peculiar greenish color. This represents the remainder of the red-blood corpuscle in which the crescent was developed.

In tertian estivo-autumnal infections the crescent is much more slender and has more pointed extremities. It very seldom shows a double outline; the protoplasm is finely granular and the pigment is large in amount and in the form of slender rods. In the quotidian estivo-autumnal infections the crescent is generally much shorter and plumper than in the tertian. Its extremities are rounded and it always presents a distinct double outline. The protoplasm is less granular and the pigment is smaller in amount and in the form of dots. Normally in the mosquito, and also in the blood which has been removed for some time from the body, these crescents undergo a series of changes, first becoming oval in shape and finally round. The spherical bodies represent, in the estivo-autumnal infections, the *macrogametocytes* and *microgametocytes* of the tertian and quartan infections and undergo similar changes in the stomach or middle intestine of the mosquito; that is, the male elements, or *microgametocytes*, become flagellated, the flagella, or *microgametes*, becoming free and fertilizing the female elements, or *macrogametes*. The male crescent, or *microgametocyte* in both species of estivo-autumnal parasites can be differentiated from the female crescent, or *macrogametocyte* by its short, plump kidney-like shape, the female crescent being longer and more slender in shape.

Cycle of Development.—Having considered the bodies which enter into the mosquito cycle, and which may be observed at times in human blood which has been removed from the body for a short time, we will now take up the cycle of development which these bodies undergo in the mosquito, bearing in mind that it is essentially the same in all varieties of the plasmodia. The process of flagellation and the fertilization of the *macrogamete*, the female organism, by the *microgamete*, or flagellum, which occurs normally in the middle intestine of the mosquito after biting an infected individual, has been described. The result of this fertilization is known as the *sporont*. After a certain period of time the *sporont* becomes elongated and finally motile, and it is then known as the *oökinete*. The *oökinete* penetrates the wall of the middle intestine and eventually becomes situated on the outer side of the epithelium and the basement membrane of the intestine between the adipose tissue and the muscular wall. Here the organism becomes spherical in shape

and forms a cyst known as the *oöcyst*. At this stage the protoplasm is granular and reticular in appearance, the pigment is reduced in amount, and the entire organism is enclosed within a well-defined capsule. The *oöcyst* is formed at about the third or fourth day after infection of the mosquito. About the fifth or sixth day the *oöcyst* enlarges and within it are formed spherical refractive bodies known as *sporoblasts*. At this stage the organism is increased so much in size that it projects from the intestinal wall. Besides the *sporoblasts*, the cyst contains some pigment and minute granules which resemble fat. At the end of a week the *sporoblasts* have produced a large number of delicate filaments having pointed extremities and containing a small amount of nuclear chromatin. These filaments are the *sporozoites*. They are about 14μ in length and are arranged in a ray-like formation about a central mass which may contain pigment. At this stage the capsule of the cyst is very distinct. The *sporozoites* are finally liberated by the rupture of the cyst and make their way to the tubules of the salivary glands. At this time the infected mosquito, when biting a man, will inoculate the *sporozoites*, which, penetrating the red-blood cells, develop into *schizonts*, and the human cycle of the organism begins. The entire cycle of development in the mosquito is about fourteen days in duration.

Briefly stated, the cycle of development of the malarial plasmodium in the mosquito may be summed up as follows:

1. *Macrogametocyte*, in tertian and quartan infections, the female spherical bodies, and in estivo-autumnal infections the female crescent.
2. *Macrogamete*, the name applied to the female elements after they are prepared for fertilization.
3. *Microgametocyte*, in tertian and quartan infections the male spherical bodies and in estivo-autumnal infections the male crescent.
4. *Microgamete*, the liberated flagellum of the *microgametocyte*.
5. *Sporont*, the result of the fertilization of the *macrogamete* by the *microgamete*.
6. *Oökinete*, the motile stage of the *sporont*.
7. *Oöcyst*, the cystic stage of the *sporont*.
8. *Sporoblasts*, developed within the *oöcyst*.
9. *Sporozoites*, developed within the *sporoblasts* and liberated by the rupture of the *oöcyst*, and which are introduced into man by the mosquito and are capable of beginning the human life cycle by infecting the red-blood corpuscles.

This cycle of development has been demonstrated in the mosquito in all varieties of the malarial plasmodia, and infection of man by the mosquito has also been demonstrated with all varieties of the plasmodia.

The Malarial Mosquitoes.—It may not be amiss to give a list of the more common mosquitoes which have been proved to transmit malarial disease. Only one subfamily, so far as we know, is capable of transmitting malaria, the *Anophelina*. Several genera belonging to this subfamily contain species which have been proved to be carriers of malaria, and the following list gives those which are transmitters of the disease:

West Indies. *Cellia argyrotarsis*. *Cellia albianus*.
 Canada. *Anopheles maculipennis*.
 United States. *Anopheles maculipennis*. *A. quadrimaculatus*. *Cellia argyrotarsis*.
 Panama. *Cellia albianus*. *C. argyrotarsis*. *Anopheles pseudopunctipennis*. *A. larsimaculata*.
 Central and South America. *Anopheles albipes*. *Pyreophorus lutzii*. *Cellia argyrotarsis*. *Cellia albianus*.
 Europe. *Anopheles maculipennis*. *A. bifurcatus*. *Myzorrhynchus pseudopictus*.
 Asia. *Myzomyia culicifacies*. *Myzomyia listonii*. *Myzomyia turkhurdii*. *Myzorrhynchus barbirostris*. *Nysorrhynchus theobaldi*. *Nysorrhynchus maculipalpis*.
 Japan. *Anopheles jesoensis*. *Anopheles formosensis*. *Anopheles cohaesus*.
 Africa. *Myzomyia funesta*. *Myzomyia nili*. *Pyreophorus costalis*. *Myzorrhynchus barbirostris*. *Myzorrhynchus pauldis*. *Cellia pharoensis*.
 Philippine Islands. *Myzomyia funesta*. *Myzorrhynchus barbirostris*. *Myzorrhynchus sinensis*. *Nysorrhynchus fuliginosus*.

Staining Reactions of the Plasmodia.—Under the section on diagnosis the staining methods which are of greatest practical use will be discussed. While the examination of the fresh blood is of the greatest importance in studying certain phases of the life cycle, the staining reactions exhibited by these organisms illustrate more fully the exact morphological structure. It may be stated that the staining reactions are similar in all varieties, and that they prove that the organism is composed of a nucleus and protoplasm. The chromatin is the only portion of the nucleus which takes the stain, and by Wright's method it stains a very brilliant red and lies, apparently, within a vesicular nucleus, the protoplasm of which does not stain. Surrounding the nucleus in the young forms is a small amount of protoplasm which stains a delicate blue color, and embedded in which is the pigment. In all the forms, as the parasite matures, the chromatin becomes distributed throughout the protoplasm, and in the full-grown parasites a distinct nucleus cannot be demonstrated, while the protoplasm stains uniformly throughout. As segmentation approaches, the pigment becomes collected more or less toward the centre of the organism, and the chromatin which has been distributed diffusely throughout the protoplasm collects into small clumps, forming a portion of the young segments. At the time of segmentation the chromatin is compactly collected in clumps lying within a minute unstained area, the vesicular portion of the nucleus, and surrounded by a small ring of protoplasm, staining very intensely. In the estivo-autumnal infections the crescents are composed, as shown by the staining reactions, of a large amount of protoplasm and a compact clump of chromatin situated at the centre or at one pole of the crescent. The flagellated organisms stain similarly to the full-grown parasites with the exception that a narrow thread of chromatin can be detected within each flagellum. This chromatin gradually becomes collected toward the centre of the flagellum before it becomes free from the parent body, the remainder of the flagellum staining a uniform blue, the chromatin being bright red in color.

In all varieties of the malarial parasite the first stage seen within the red cell in stained specimens is ring-shaped, consisting of a small dot of chromatin surrounded by an unstained area, and this again surrounded by a small amount of protoplasm. The diagnosis of malarial infections

is much easier when stained preparations are used than when the blood is examined in the fresh condition.

Contributing Factors.—While the malarial parasites are the direct cause of the malarial infections, and while the transmission of the disease depends entirely, so far as we at present know, upon mosquitoes belonging to the *Anophelinæ*, there are certain factors which enter indirectly into the etiology. These favor the development of the parasites within the body or indirectly aid in infection. Among them are the following:

Locality.—This has a decided influence upon the character of the infection. The mild tertian and quartan infections, especially the tertian, are of almost world-wide distribution, but the more severe estivo-autumnal types are much more limited as regards locality, being very uncommon in northern latitudes and becoming more and more common as the tropics are approached.

Climate.—These infections are most common and pernicious in tropical climates, so that heat may be considered as an essential predisposing cause. Even in temperate climates, the estivo-autumnal fevers prevail mostly during the summer and autumn months, while in the tropics they prevail throughout the year. Thayer and Heweston¹ called attention to the seasonal variation in Baltimore. The smallest number of cases occurred during the months of December, January, and February; during the spring months the cases increased until May, and then decreased until July, when they again increased and reached the maximum in September. The observations of these authorities have been borne out by numerous investigators, and there can be no doubt that the season has a most marked influence. This is probably due to the fact that mosquitoes, especially in temperate climates, are much more numerous during the summer and autumn months.

Time of Day.—It has always been observed that there is much more danger of contracting malaria at night than during the day. This is easily explained, for mosquitoes usually bite during the night.

Altitude.—These diseases occur especially in lowlands along the coast and rivers of warm countries. Mountainous regions are generally free from malaria, although this is not always so, for in the Philippine Islands certain valleys are almost free, while the hills in the vicinity are notoriously infected. Persons living in the tropics and sleeping in the lower stories of houses are more apt to become infected with malaria than those in the upper stories. The explanation is that, as a rule, mosquitoes do not fly to any great height.

Moisture.—Marshes and low-lying damp regions are usually conducive to malaria, and moisture is a most important factor in the distribution of the disease. This is again explained by the fact that mosquitoes are most numerous in moist regions. Rain favors the production of malaria because it favors the breeding of the mosquito.

Soil.—Tropical jungles, low marshy islands, or lands covered with pools of stagnant water have always been regarded as conducive to

¹ *Johns Hopkins Hospital Report*, 1895, v, 5-215.

malarial infection. The soil *per se* has nothing to do with the production of malarial disease except insofar as it favors the breeding of mosquitoes. A moist soil favors the spread of the disease, as it brings about the conditions favorable for the development of the mosquito larvæ; this is also true of those instances in which malarial epidemics have followed the upturning of soil in certain localities, thus favoring the formation of stagnant pools in which the larvæ of the mosquito develop.

Race.—According to Thayer and Hewetson, the negro is less liable to contract malaria than the white man. This subject has attracted the attention of a great many investigators, and it has been found that the native negro races acquire a more or less complete immunity in early life from malarial disease. A very large percentage of negro children in infected localities are found to harbor the malarial plasmodia, but this is not true of the adult. There is probably no racial immunity against malaria, but an acquired immunity is present among many people who inhabit malarial regions.

Age.—Children are more susceptible than adults, probably due to the fact that mosquitoes bite children in preference to adults.

Sex.—When equally exposed, both sexes have the same ratio of infection, but malaria is more common in men than in women, as the latter are not as often exposed to the bites of the mosquito.

Occupation.—The occupation of man becomes a predisposing factor in the production of the disease in proportion to the chances that occupation gives him of infection by the mosquito. Laborers working at ditching, railway building, and other occupations which necessitate the turning up of the soil and exposure to night air, and therefore to the bites of mosquitoes, are especially liable to contract the malarial fevers.

There are numerous other factors which contribute to the production of malarial fevers, among which may be mentioned those which lower the individual's resisting powers, such as exposure, dissipation, over-eating, overwork, whether mental or physical, and, in short, anything which interferes with the normal physiological processes. There can be no doubt that an infection with a small number of malarial parasites is overcome, in a great many instances, by the healthy individual, but should the normal resisting powers be lowered such an infection would result in the symptoms of the disease.

Cultivation.—The first investigator who claimed to have cultivated the malarial plasmodia was Coronado,¹ but his experiments have been repeated by other observers, none of whom have been able to confirm them. The estivo-autumnal parasites have been kept alive outside of the human body for some days. Sakharov was the first to perform such experiments, and he was able to keep the parasites alive in blood, obtained by leeches from the human subject, for a week. No reproductive changes, however, were observed. The recent work of Bass has demonstrated that it is possible to cultivate the malarial parasites in blood to which dextrose has been added and he has succeeded in thus cultivating them through four generations.

¹ *Cronica Medici Suirurgica de la Habana*, 1892, v, 215.

Inoculation Experiments.—The malarial fevers may be transmitted by direct inoculation from man to man. It has invariably been found that the type of parasite inhabiting the blood injected is found again in the blood of the individual infected, and is followed by the clinical symptoms of the variety of malaria produced by the type of parasite injected.

Immunity.—This may be considered under the following heads: racial, congenital, and acquired immunity. Natural immunity may occur, but it is undoubtedly rare.

Racial Immunity.—Certain races of mankind have been considered immune to the malarial fevers. This statement, however, rests upon but very little proof, and cannot be substantiated by facts. Some races are more resistant to malaria than others; for instance, the black races are more resistant in adult life, but the immunity which exists is undoubtedly acquired. In other words, in those races which live in malarial localities the disease is acquired in very early life and a natural immunity is established so that the adult individuals are resistant to the infection.

Congenital Immunity.—There exist people, living in the most malarious localities, who have never suffered from the disease. This immunity is, in all probability, congenital, and in a few instances has been proved to be a family characteristic.

Acquired Immunity.—Long residence in a malarious country may confer a relative immunity. Repeated attacks will in time render the individual less liable to further attacks. We can explain this in only one way: that the malarial poison produces certain changes in the human organism which render it at least partially immune to future attacks. The history of acquired immunity is simply that of repeated attacks of malarial fever, each one a little less severe than the preceding, until at last a spontaneous permanent cure results. Such immunity may be lasting, but as a rule hardship, privation, ill-health, or removal to a new locality will destroy it.

Pathology.—Primarily, malarial infections exert the most marked effect upon the blood, as the plasmodia live at the expense of the red-blood corpuscles, and probably elaborate toxins which materially affect all the elements of this fluid. In 1847, Meckel discovered granules of pigment in the blood, and ever since then the condition of melanemia has been recognized as one of the most characteristic features of malarial disease. The pathological changes which occur in the blood are the result of primary and secondary causes, the primary cause being the infection of the red cells by the parasites and the changes brought about by such infection; the secondary, the anemic condition which is the inevitable result of malarial infection.

Macrophages occur in the blood, containing much pigment, and especially in the estivo-autumnal infections, numerous plasmodia. Together with these there occurs either free or within many of the leukocytes, brown, black, or brownish-yellow pigment, occurring as blocks, granules, rods, grains, and irregular clumps. The occurrence of this pigment is one of the most characteristic conditions in the blood of malaria. The pigment occurs in two forms, *melanin* and *hemosiderin*.

The first gives no reaction for iron, while the second does. As regards the origin of the two varieties Bignami has well said:

"The melanemia, index of an acute infection, is derived only from the direct transformation of hemoglobin into *melanin* through the action of the parasites within the red-blood corpuscles; the melanosis of the viscera, spleen, liver, bone-marrow, etc., index of a previous infection, has a double origin. In chief part it is derived from the melanemia; that is, from the disposition in the viscera of the black pigment (*melanin*) formed during the acute infection in the circulating blood; in part it has a local origin, that is, it is derived from the slow transformation of the blocks of yellow-colored pigment (*hemosiderin*), which are deposited or formed in the spleen and in the other viscera from the enormous quantity of altered red blood corpuscles, which, in grave infections, die before the direct action of the parasites has transformed their hemoglobin into black pigment."

Besides the occurrence of changes in the form and color of the red-blood corpuscles, as well as the occurrence in the blood of pigmented leukocytes and pigment, in all forms of malarial fever there is a reduction in both the red and white corpuscles. This reduction is very often more marked in tertian and quartan malaria than in estivo-autumnal, and is due to the action of the parasites upon the corpuscles containing them, the action of the poisonous material elaborated and set free by the parasites, and to inhibited function of the blood-producing organs.

Kelsch¹ found that a reduction followed every paroxysm of the fever. This reduction may be very great; some cases have been observed in which only 500,000 red cells were present to the cubic millimeter. In ordinary cases, after the infection has persisted for a few days, it will be found that the red cells have fallen to 2,000,000, or slightly less, per cubic millimeter. This marked reduction, however, is not persistent, for in long-continued infections it will be found that after a certain amount of anemia has been produced there is no further fall, and even in most cases a slight gain over the lowest point reached during the acute infection. In the pernicious forms the red cells may fall to 1,000,000 or less per cubic millimeter within twenty-four hours, but if the patient has suffered from repeated attacks such a marked decrease is but seldom observed. The return to the normal number of red cells is generally rapid after the mild, and in some cases after severe infections which have been promptly stopped by treatment; but in cases which have been treated improperly or in which many relapses have occurred a chronic and persistent anemia is produced.

In severe cases nucleated red cells are sometimes seen and poikilocytosis is almost invariably present. In such cases the polymorphonuclear leukocytes are decreased while the mononuclear are increased.

As regards the white corpuscles, it may be said in general that the reduction in their number corresponds with that of the red cells. During the paroxysm there is often a leukocytosis, while between the paroxysms the leukocytes are markedly reduced in number. This is, in general,

¹ *Archives de physiologie*, 1875, viii, 690.

true of all forms of malarial fever, but in some cases of fatal pernicious malaria a leukocytosis is observed. Recently much attention has been paid to the relative increase in the mononuclear leukocytes as being of diagnostic importance in malarial infection. While probably in a majority of instances there is a considerable increase in this type of cell, it has not been the writer's experience that very much weight can be given in diagnosis to a mononuclear increase, as it occurs in so many conditions that are not malarial in nature.

Besides the reduction in the red and white corpuscles there is generally a marked reduction in the hemoglobin, especially in the estivo-autumnal infections. This reduction may be very rapid, the hemoglobin falling from 10 to 40 per cent. within two or three days. But little weight can, however, be given to this as regards the prognosis of individual cases. In some of the most pernicious forms there may be but a slight reduction, while in many benign tertian infections it is often very marked.

The Urine.—In many cases of benign tertian and quartan malarial infections there is but little change in the urine, but in the more severe estivo-autumnal infections there is often a marked reduction in the amount during the apyrexial stage, while during the paroxysms the amount is increased. *Polyuria* is often marked during the convalescence from tertian and quartan fevers but is not so common in the estivo-autumnal infections. Sometimes the polyuria is very excessive. One patient observed by the writer, after a tertian estivo-autumnal attack, passed from 20,000 to 25,000 cc. of urine per day. The *color* is generally dark amber or reddish, and the *acidity* is increased when the urine is diminished in amount. The *specific gravity* is increased during the attack, but in cases showing polyuria it is generally very low, being from 1.005 to 1.010. The amount of *urea* excreted in twenty-four hours is increased, especially during the paroxysm, but in cases showing polyuria the amount is generally decreased. The *chlorides* are not increased as a rule. *Albumin* appears in a certain proportion of very severe tertian and quartan infections and in the majority of estivo-autumnal infections. In the latter class of cases hyaline and granular *casts* are often observed, and it can be stated as a rule that all fatal cases of malaria show albuminous urine containing casts prior to death. Personal observations suggest that *indican* is almost invariably increased in the urine of patients suffering from estivo-autumnal infections. An acute nephritis is observed in from 4 to 5 per cent. of severe estivo-autumnal infections, and in an occasional case of tertian and quartan malaria.

Morbid Anatomy.—A patient dead of malarial fever presents a peculiar brown or grayish hue of the *skin*. The degree of emaciation depends upon the duration of the infection. Rigor mortis is moderate, and post-mortem discoloration occurs early and may be very intense. As most cases of pernicious malaria die from cerebral complications, the *brain* presents most marked pathological lesions. Externally the bloodvessels are much congested, the entire organ appearing hyperemic. Small capillary hemorrhages are often observed and œdema is the rule. In cases in which no brain symptoms have been exhibited during life, the organ externally shows but little hyperemia. The changes in the

brain consist in congestion of the capillaries and the presence of minute hemorrhages within the substance of the organ. The congestion and hemorrhages are due to blocking of the capillaries by malarial parasites, which may be observed in various stages of development within the red cells, together with an immense amount of pigment and numerous pigmented leukocytes. Very often the pigment is present in such large amount that the organ appears pigmented upon naked-eye inspection. The parasites may be so numerous that there are hardly any uninvaded corpuscles seen, or they may be few in number. Microscopically, it may be found that many of the capillaries in the severe infections are entirely filled with red cells containing parasites, and often thrombi are formed, composed of such corpuscles, together with pigment and pigmented leukocytes. Besides the infected blood corpuscles free parasites may be observed, as well as macrophages, free pigment, pigmented leukocytes, and endothelial cells. In the nerve cells in estivo-autumnal infection, changes occur both in the protoplasm and nucleus of the nerve cell and lead to a complete degeneration. Guarnieri has described the changes occurring in the *retina* in pernicious malaria, finding hemorrhages and congestion of the capillaries, leading to impairment of function.

The changes in the lungs are not at all characteristic, varying considerably according to the stage of the disease, and being those usually found in severe fever. A microscopic examination of sections in certain cases shows congestion of the alveoli, which contain large numbers of pigmented, parasite-laden, white cells, and infected red-blood corpuscles. In those cases in which bronchopneumonia has occurred, the exudation in the alveoli is mostly composed of the polymorphonuclear leukocytes, together with numerous infected red-blood corpuscles and pigment, although the free pigment is generally small in amount. A pneumonia complicating a fatal attack of malarial infection, is without doubt due to a double infection by the pneumococcus and malarial plasmodium.

No changes which are characteristic are observed in the heart muscle.

There has been considerable discussion regarding the changes occurring in the *stomach* and *intestine* in pernicious malaria. In certain cases in which diarrhoea has been marked some time before death, the mucous membrane of these organs is more or less pigmented and there is marked hyperemia, and even necrosis and ulceration. The Peyer's patches, as well as the solitary glands, are often swollen. Upon microscopic examination, sections of the stomach and intestine show that the capillaries of the mucous folds are often crowded with parasite-invaded corpuscles and these may occlude the capillaries, resulting in necrosis and ulceration of the mucous membrane.

The liver is generally enlarged and markedly pigmented and in some cases almost black in color. Upon section, the cut surface is often very much pigmented and generally greatly congested. Microscopically the most marked changes are found in the capillaries and liver cells. The capillaries show many very large phagocytes containing much pigment and sometimes infected red-blood corpuscles, as well as malarial parasites. The epithelial cells are greatly swollen and may contain free pigment and degenerated organisms. Free pigment is often observed in

large lumps within the liver capillaries, while the stellate cells of Kupfer present marked pigmentation. The liver cells are atrophied, undergoing fatty degeneration, necrosis, and pigmentation. The pigmentation in the liver cells is not due to the malarial pigment but to pigment derived from degenerated red-blood corpuscles and is not characteristic of malaria. Areas of focal necrosis occur, believed by Flexner to be due to some circulating toxic substance.

The organ which presents probably the most marked changes is the *spleen*. It is almost invariably enlarged, sometimes enormously so. It is of a dark blue or almost black color externally, the capsule being smooth, while upon section the cut surface is of a chocolate, slate, or almost black color, the consistence being very greatly decreased. The Malpighian corpuscles are almost invisible. Upon microscopic examination the capillaries are found greatly congested by multitudes of red-blood corpuscles, most of them containing parasites. This is not always true, as there are numerous cases in which few infected red-blood corpuscles are demonstrable in the spleen. The intense congestion of the capillaries pushes apart the cells of the splenic pulp, and in some cases large areas are destroyed by hemorrhagic exudation. In the spleen the red cells contain parasites in all stages of development, but the pigmented forms and the segmenting bodies are most commonly observed, as well as the crescents in estivo-autumnal infections. Besides the infected red-blood corpuscles, sections of the spleen show an immense number of phagocytes. These leukocytes consist of small cells which resemble lymphocytes, and larger cells known as macrophages. The macrophages contain clumps of pigment, red-blood corpuscles containing parasites, free parasites, degenerated red-blood corpuscles, and even the small phagocytic cells which have been mentioned. The Malpighian bodies do not become pigmented but the fibrous trabeculae always present marked pigmentation. The free pigment is present in the form of small rods or granules. Here, as in the liver, two forms of pigmentation occur, the dark brown or nearly black melanin, the malarial pigment, and the golden yellow pigment, or hemosiderin, derived from degenerated red-blood corpuscles.

The *kidneys* in pernicious malaria present very marked lesions which have been studied especially by Ewing and Dock, who have contributed very valuable work upon this subject. The condition produced is generally that of an acute nephritis, presenting all the typical lesions of this disease, together with the peculiar lesions due to malarial infection. As in the liver and spleen, microscopically the most marked change is the great congestion of the capillaries of the Malpighian tufts and the inter-tubular capillaries. These vessels are filled with infected red blood corpuscles, free pigment, and pigmented leukocytes. There is also present a marked pigmentation of the endothelial and epithelial cells, as well as those lining the tubules. Free parasites are often observed and may be seen occasionally within the glomerular capillaries. The epithelium of Bowman's capsule is undergoing marked proliferation and the capillary space may be entirely occluded. The epithelium of the tubules presents marked degenerative changes, consisting of fatty and albuminoid degen-

eration and necrosis. The straight tubules often contain hyaline, epithelial, or granular casts. There is not a marked pathological condition of the kidneys in every case, but it is safe to say that most cases of pernicious malaria are accompanied by an acute parenchymatous nephritis.

In certain cases the *bone-marrow* presents marked changes. Microscopically, unless the malarial infection has persisted for a long time, there is but little change. If weeks or months have elapsed, however, the color changes from the normal yellow to red or dull black. The capillary vessels are found to contain numerous endocorpuseular parasites in various stages of development, and in estivo-autumnal infections, crescentic bodies. They also contain numerous macrophages, and in the marrow-pulp are found free parasites in various stages of development, as well as macrophages, nucleated red-blood corpuscles, and pigmented medullary cells.

All the changes described are not presented, as a rule, in every case. Some cases will present marked changes in the spleen and liver, while the brain and kidneys are but slightly affected, and in others all the chief viscera of the body will show marked lesions. The pathology of chronic malarial infection, or malarial cachexia, is characteristic. There is always a marked anemia, the spleen is greatly enlarged, sometimes weighing ten or more pounds, and presents marked pigmentation. The liver is also enlarged but not in proportion to the enlargement of the spleen. This organ also appears pigmented. The kidneys are enlarged and grayish in color, due to deposits of malarial pigment. This is also true of the brain cortex, and upon section of the brain there is marked congestion of the capillaries, which contain numerous infected red blood corpuscles, pigmented leukocytes, and free pigment. The condition present is characterized by the marked pigmentation of all the viscera, to which the name melanosis may well apply.

Pathology of Latent Malarial Infection.—By this term we mean cases in which no symptoms of malaria are presented, but which have died from some other disease. During my service in the U. S. Army General Hospital, Presidio of San Francisco, California, seven cases were observed in which the autopsy showed latent malarial infection; during life no symptoms of such infection had been presented. In three of these the infection was tertian in character, and in four, estivo-autumnal. The pathology of these cases is interesting as showing the lesions produced before the disease could be diagnosed. The pathological lesions found were confined entirely to the spleen and liver. The spleen in the tertian infections was considerably enlarged and somewhat pigmented. Microscopically the sections showed intense congestion of the sinuses, together with pigmentation, especially marked along the edges of the Malpighian bodies and the fibrous trabeculae. Many of the cells of the splenic pulp were pigmented. In the splenic sinuses and in the capillaries there were numerous parasite-infected red cells and pigmented leukocytes, but such cells were not nearly as numerous as in acute infections. The parasites were characteristic of those occurring in the peripheral blood and were all in about the same stage of development in each case. While this was so, it happened that the patients died at

such intervals that the entire human cycle of the tertian parasite could be worked out from an examination of sections of the spleen, and the chief point of importance in the pathology of latent infections, as observed in these cases, is that the entire human cycle of the parasite can be followed in the spleen when no parasites are demonstrable elsewhere in the body, proving conclusively that the seat of the initial infection is in the spleen. The capillaries also contain numerous pigmented leukocytes and macrophages.

The *liver* in the tertian infections did not differ in appearance from that of the normal organ, but upon section the capillaries showed within them a few pigmented leukocytes, some containing what appeared to be degenerated malarial organisms. No infected red cells were observed.

In the estivo-autumnal infections the pathological lesions were the same and the life cycle of the parasite could be traced from the earliest hyaline organism to the segmenting bodies, but no crescents could be demonstrated. The only explanation of this fact is that the parasites had not advanced to the stage in which crescent formation was possible.

Symptoms.—Incubation.—This has received a great deal of attention, but there is considerable confusion regarding it. Marchiafava and Bignami found that the incubation period, from the time the patient was bitten by the mosquitoes until the first symptoms appeared, varied from nine to ten days. From inoculation experiments, Bastianelli and Bignami found that in estivo-autumnal infections the maximum period of infection was five days, the minimum two, and the mean three days. Mannaberg in seven cases found the period of incubation to vary from three to fourteen days, while Marchiafava and Bignami found the maximum to be fourteen days and the minimum two. As regards the data obtained from inoculation experiments, it may be stated that the disease was inoculated in an unnatural manner, and for this reason the data may be unreliable. In inoculation of blood containing only the forms of the parasite belonging to the human cycle it is reasonable to suppose that the period of incubation will be shorter than is the case when the mosquito transmits the *sporozoites* to man, and this has been proved experimentally, for Marchiafava and Bignami have found that in an individual stung by a mosquito which had sucked blood containing crescents, estivo-autumnal fever developed in from nine to twelve days, whereas in the inoculation experiments of all the authorities quoted the mean was six days. But though the period of incubation of these fevers is doubtless in the majority of cases from nine to twelve days, numerous instances do occur which show a much longer period of incubation, sometimes weeks or months. The period of incubation may be very much prolonged, and in authentic instances personally observed the first symptoms of malaria did not appear until from seven to ten months after exposure. These were in the person of officers and enlisted men of the army serving in a tropical climate, exposed to estivo-autumnal fever and who immediately afterward were stationed in localities in which there were no *Anopheles* mosquitoes and no endemic foci of malaria.

The explanation of these long periods of incubation is made clear by the theory advanced by Thayer, *i. e.*, that the parasites multiply and

undergo their life cycle, but in such small numbers that they give rise to no observable clinical signs. Or it may be that latent forms are produced which remain inactive for long periods of time.

Although many individuals in malarial localities do not present symptoms of malaria for long periods of time, it is without doubt true that in the great majority of instances an individual exposed to infection will acquire the disease in from three weeks to two months. This was well illustrated in the case of our soldiers in Cuba, almost 95 per cent. of whom gave a history of being there from two to six weeks before the onset of malarial fever. One month was the most common period intervening between landing in Cuba and the first chill.

The length of the period of incubation will vary with the amount of the infecting agent, the physical condition of the infected individual and his surroundings as regards exposure, heat and cold, nourishment, etc.

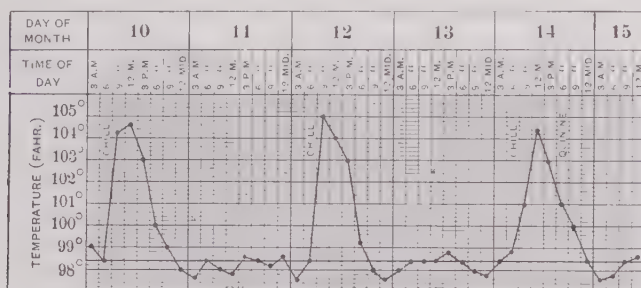
Classification.—It is extremely difficult to classify the malarial fevers from a clinical standpoint. A division into intermittent, remittent, and continuous fevers, while useful, is at best but a rough classification which does not signify disease entities and is confusing in many ways. Any malarial fever may be intermittent, remittent, or continuous. For instance, while a single tertian infection is undoubtedly intermittent we can conceive of a tertian infection in which several generations of parasites may mature at various times, giving rise to a remittent or even continuous temperature curve. The same is true of quartan, and especially of the estivo-autumnal infections. It is also true that infection with one generation of any of the malarial plasmodia will always result in a typical intermittent fever. In other words, *all* malarial infections are intermittent in character and only become remittent or continuous when more than one generation of the plasmodium matures at different intervals of time. While the term remittent malaria is generally applied to infections due to the estivo-autumnal parasites, the name is a misnomer, as the estivo-autumnal infections are as truly intermittent as are the tertian and quartan. For this reason it seems better to classify the malarial fevers from an etiological standpoint, *i. e.*, tertian, quartan, and estivo-autumnal.

Symptoms of Tertian Malaria.—The paroxysms of fever in tertian malaria occur every forty-eight hours and are due to the segmentation of the tertian malarial plasmodium. The time of the paroxysm can be accurately judged by the stage of growth of the organism as seen in the peripheral blood. The onset of the paroxysm always occurs during the sporulation of the organism, and daily paroxysms are caused by double infections with the tertian parasite.

This, the most common and mildest form of malarial fever, occurs both in tropical and temperate climates, and when uncomplicated, presents a typical temperature curve, showing in single infections a rise of temperature every second day, while infections with numerous groups of tertian organisms may give rise to a remittent or subcontinued fever. In cases which present daily paroxysms it is often possible to destroy one group of parasites by small doses of quinine, and, when this is done, the regular tertian paroxysm will reappear.

The paroxysm, when typical, is divided into three stages, chill, fever, and sweating. The *prodromal* symptoms are generally malaise, loss of appetite and more or less dull headache. After these symptoms have persisted for a few days the patient is seized with a severe chill, but although he feels extremely cold the temperature continues to rise and at the acme of the chill has reached 103° , 104° , or even 106° F. The chill is immediately followed by a pronounced sense of heat, and in a short period of time the patient will complain as bitterly of this as he previously did of the cold. During the stage of fever, delirium is often present, accompanied by severe headache. During the onset of the chill, nausea and vomiting are common, but they do not persist, as a rule, during the stage of fever. After the fever has lasted for a few hours, it rapidly declines to normal, accompanied by very severe sweating.

FIG. 1



Tertian malarial fever.

The Cold Stage.—There are generally some prodromal symptoms of the approaching malarial chill, as evidenced by yawning, a general sense of discomfort, headache, and often nausea and vomiting. The feeling of cold usually commences at the feet and gradually progresses upward, although very often the first chilly sensations are felt along the spine. In this form of infection the chill is severe, the patient shaking very vigorously, but it is not so severe as in the quartan infections. In certain mild cases the chill may be absent, the patient complaining only of chilly sensations. The facial expression during the chill is one of cyanosis, the lips being blue and the skin bluish-red in color. The extremities are cyanotic and the skin presents the well-known condition characterized as “goose flesh.” The pulse is rapid, generally rather diminished in volume and often irregular. Headache is very often intense. During the chill the temperature rises very rapidly, reaching 104° F. or more, but careful examination will demonstrate that it has begun to rise before the onset of the chill. The urine is increased in quantity and lowered in specific gravity. The duration of this stage varies from one-quarter of an hour to two hours in the most severe cases.

The Hot Stage.—At the commencement of the hot stage the patient complains of flushings of heat, rapidly succeeded by cold sensations. Soon the sensations of cold are entirely lost and the patient complains

of the intense heat occasioned by this high temperature. The facial appearance is that of congestion, the conjunctiva being injected and the skin red, while the entire surface of the body is reddened and the congestion is especially marked in the hands. The pulse is full, bounding, and often dicrotic. The respirations are often rapid and hurried, and there may be more or less cough, denoting congestion of the lungs. The headache increases and may become very intense and of a throbbing character. Epistaxis occurs in a small proportion of the cases. In the milder tertians there are no nervous symptoms present beyond a severe headache, but in the severe cases there may be marked delirium or a drowsy condition merging into a semicoma. This condition is almost always present in those rare cases of tertian infection which become pernicious. The chief symptoms complained of during the hot stage are the severe headache and the intense heat. The temperature may reach its extreme height during this stage but very often the height of the fever is reached at the end of the cold stage. It is not uncommon during the hot stage to observe cutaneous eruptions. Herpes is very frequent especially on the lips, and urticaria and a general erythema not infrequently occur. These eruptions sometimes lead to a suspicion of some eruptive disease being the cause of the chill. Herpes of the penis may occur. The duration of this stage varies somewhat, but is generally from four to six hours.

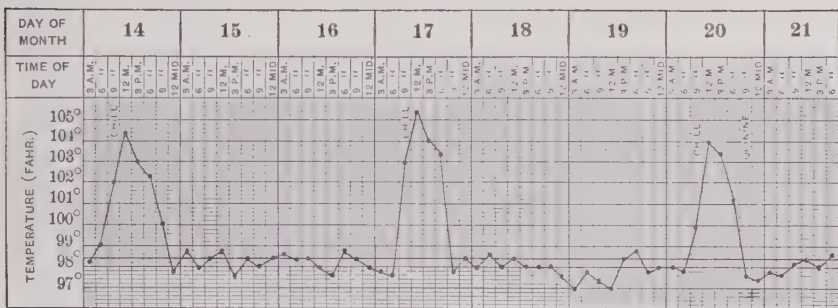
The Sweating Stage.—As the fever begins to decline, it will be noticed that the perspiration appears first on the forehead and face, and the patient at once begins to feel better, the decrease in the unpleasant symptoms being proportionate to the severity of the sweating. Commencing on the face, the perspiration rapidly involves the entire body and is often so severe that water may be seen trickling from the skin of the arms, thighs, and legs. The sweating stage lasts, as a rule, from two to three hours, at the end of which time the temperature has declined to normal, all of the unpleasant symptoms have disappeared, and the patient generally sleeps for some time. As a rule, the temperature goes somewhat below normal and the decline is accompanied by considerable weakness of the circulation, the pulse being slow and weak. In very rare cases this stage may be accompanied by collapse, and in one case of pernicious tertian infection observed by the writer this collapse proved fatal. During the cold stage an excessive amount of urine is often voided, polyuria being a most frequent symptom.

The average duration of the entire tertian paroxysm is from eleven to fourteen hours, but it must be remembered that there are paroxysms so slight as to be hardly recognized, especially in children, while, on the other hand, the length of the paroxysm may be prolonged to twenty-four hours. In children the onset is often accompanied by convulsions.

Physical examination will generally show an enlarged spleen, but this sign cannot be relied upon except in those cases which have severe and repeated infections. Albuminuria is present in a considerable proportion of the cases. Of over 1000 cases of tertian infection personally observed nearly 400 showed albumin in the urine, and 86 showed the presence of a few granular and epithelial casts.

Symptoms of Quartan Infections.—The quartan paroxysms occur every seventy-two hours, but here, again, we may have double infections in which the sporulation of the parasites occurs at irregular intervals, thus giving an irregular temperature curve. It is not necessary to detail the symptoms occurring with quartan paroxysms, as they differ in no way from those occurring in tertian infections except that, as a rule, they are more severe and these infections are more apt to become pernicious. There are the same stages of chill, fever, and sweating as are seen in the tertian infection. The nervous symptoms are very much more pronounced, the headache being more severe, and slight delirium being almost always present. The quartan paroxysm is not as prolonged as the tertian, seldom covers more than ten hours, and is due to the sporulation of the quartan parasites.

FIG. 2



Quartan malarial fever.

Symptoms of Estivo-Autumnal Infections.—Clinically, all estivo-autumnal infections should be classed as severe infections, in contradistinction to the quartan and tertian infections, which are usually considered as mild infections. It should be thoroughly understood, however, that a quartan or tertian infection may become pernicious, although such instances are rare. The old idea that there is a malarial parasite peculiar to the pernicious infections is no longer tenable, for it is now recognized that any of the malarial parasites may induce pernicious symptoms, and that the parasites accompanying such infections do not differ in any respect from those accompanying the mildest infections.

The estivo-autumnal infections occur in temperate regions most frequently during the months of July, August, September, and October, but in the tropics they persist throughout the year, and are not characterized by any marked seasonal prevalence.

The writer believes that these infections are caused by two distinct varieties of the estivo-autumnal parasite, one completing its cycle of development in the human body in twenty-four hours, and the other in forty-eight hours. Either of these parasites is capable of causing pernicious infections, but personal observations suggest that the tertian estivo-autumnal parasite is the one most commonly concerned. From

personal observations embracing nearly 2000 cases of estivo-autumnal fever in which the parasites were demonstrated in the blood, 75 per cent. were due to the tertian estivo-autumnal variety.

The estivo-autumnal infections have long been distinguished by the term remittent, it being supposed that in these infections the temperature curve, instead of presenting the marked intermittency observed in tertian and quartan infections, was remittent or irregular in character. This is, however, not always correct, for these infections, when uncomplicated or uninfluenced in any way by treatment, may be as truly intermittent as are the tertian and quartan infections. It is undeniable, however, that remittency and irregularities in the temperature curve are more common in the estivo-autumnal infections, but too much stress should not be laid upon this point in diagnosis.

Symptoms of Tertian Estivo-autumnal Fever.—Patients suffering from this variety will present, as a rule, the following symptoms:

Prodromal.—The prodromal symptoms are loss of appetite, slight headache, evanescent pains in the back and legs, nervousness, increased urination, and a general feeling of malaise. As in the tertian and quartan infections, three stages may be distinguished.

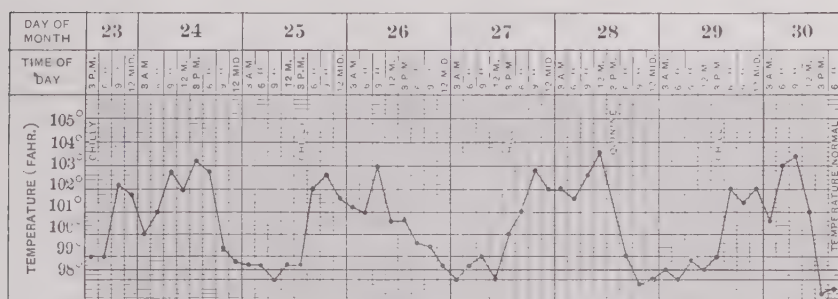
The Cold Stage.—This commences with yawning and the patient complains of headache, slight nausea, perhaps accompanied with vomiting, and often intense nervousness. In a majority of cases there are no distinct chills, but the patient complains of creeping sensations along the spinal column and slight flushings of cold especially noticeable along the posterior portion of the buttocks and thighs. At the same time the headache increases and there is generally profound mental depression. The mucous membranes are cyanosed and the extremities cold. There is severe pain in the legs and back, greatest, as a rule, in the lumbar region. The pulse is generally weak and increased in frequency and may be very irregular. The respirations are rapid and rather shallow. During this stage the temperature is elevated and may reach 103° F. or more. This stage does not last over half an hour in a majority of the cases.

Hot Stage.—The patient next experiences a sense of heat which comes first as localized flushings, but soon becomes general. The facial expression is that common to fever, the eyes being suffused and brilliant, the face red, and the skin hot and dry. Headache is intense and there is present either great mental depression or nervous excitement. The pain in the back and limbs is often agonizing in character, and in some instances there is severe pain over the abdomen. The temperature is elevated and the curve very characteristic. Nausea and vomiting are often present, vomiting being sometimes very severe. The urine is increased in quantity and is generally albuminous. Diarrhœa is a common complication. The pulse is rapid and dicrotic in character, the respiration rapid, and there may be severe dyspnœa. This stage lasts for several hours, often from sixteen to eighteen or twenty, and is succeeded by a stage of remission. During this time the symptoms gradually decline in severity and finally disappear, the temperature returns to normal, generally going a degree or degree and a half below normal. A slight sweating occurs, but this is not nearly so marked as in the tertian and

quartan paroxysms. The intermission may last only two or three hours when another paroxysm ensues. As a rule, attacks of this fever occur toward evening, extend throughout the next day, and subside during the first hours of the third day, the entire paroxysm thus lasting thirty-six hours or more and occurring every forty-eight hours.

While the symptoms described are often more severe than they are in the tertian and quartan infections, there is nothing diagnostic about them except the temperature curve. In uncomplicated cases the behavior of the temperature is absolutely characteristic, and the temperature curve is one that is not met with in any other disease. This peculiarity of tertian estivo-autumnal infection was first pointed out by Marchiafava and Bignami, and the writer has confirmed their observations in every uncomplicated case of such infection. At the onset of the fever the temperature rises suddenly to 103° or 104° F. Following the sudden rise there occurs slight oscillation which covers several hours, during which time the temperature falls from $\frac{1}{2}^{\circ}$ to 1° . This

FIG. 3



Tertian estivo-autumnal fever.

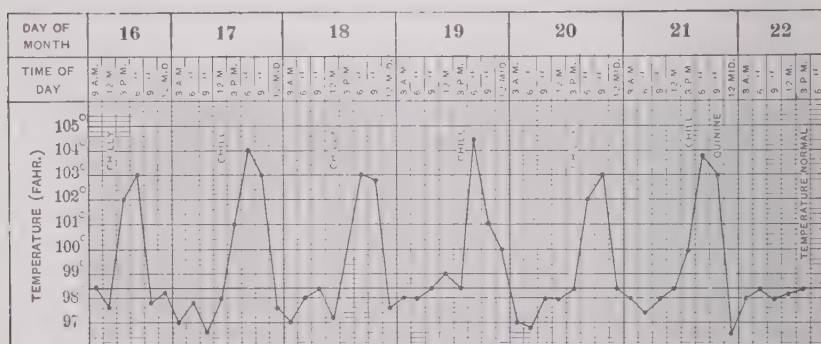
period of oscillation is followed by a distinct fall or pseudocrisis, the temperature dropping from $1\frac{1}{2}^{\circ}$ to 2° , or even 3° . This fall of temperature is often considered by the physician as the true crisis of the paroxysm, but the fever again rises to a point higher than before and then falls rapidly. This is the true crisis, as the temperature goes below normal. This temperature curve can be divided into five stages: (1) the initial rise; (2) the period of slight remissions; (3) the pseudocrisis; (4) the precritical stage; (5) the true crisis.

Another point of value in diagnosis between this type of fever and the mild tertian and quartan types is the length of time during which the fever lasts. This varies, but generally the temperature remains elevated over twenty-four hours, and often from thirty-eight to forty; in other words, the paroxysm really covers two days, while the period of intermission is very short. While this peculiar temperature curve is observed in a very large proportion of cases of tertian estivo-autumnal malaria, there may be many deviations from it due to several factors, among the most important being improper medication, double infections, or

infection with more than one variety of malarial parasite; anticipation of the attacks or retardation, which are especially common in the pernicious forms; and slight elevations of the temperature occurring between the paroxysms. The ordinary temperature chart which shows only the morning and evening temperature is worse than useless as a guide in studying this form of fever. The temperature should be taken at least every four hours and better every three.

Symptoms of Quotidian Estivo-Autumnal Infections.—The quotidian infection, which depends for its etiology upon the quotidian form of the estivo-autumnal parasite, varies but slightly in its symptomatology from the tertian, except that the paroxysms occur every twenty-four hours. As a rule, in the quotidian cases the chilly sensations are more severe and there is often a distinct chill. Sweating is also more pronounced but is not so marked as in the simple tertian and quartan fevers. The temperature curve is entirely different. It consists in the abrupt

FIG. 4



Quotidian estivo-autumnal fever.

rise of the temperature to 103° F. or more, succeeded by as abrupt a fall. The attack lasts as a rule only about eight or ten hours. The temperature curve seldom remains regular for long at a time, for the attacks tend to run into one another, thus giving rise to a continuous fever. This is especially true of those cases of a pernicious type. The temperature curve in the quotidian form is not characteristic as it resembles very closely that of double tertian infection.

Pernicious Malarial Infections.—Any one of the malarial plasmodia may give rise to pernicious symptoms, but the vast majority of fatal cases of malarial fever are due to the estivo-autumnal parasites. The tertian estivo-autumnal parasite is more often concerned in such infections than is the quotidian, but it should be remembered that the tertian infections are very much more numerous than are the quotidian. It is very important in treating cases of estivo-autumnal malaria to remember that there is always an element of danger in that they may at any time develop pernicious symptoms which may cause death, and it

should be distinctly understood that the pernicious forms depend for their etiology upon the same organisms as do the mildest forms.

The great majority of pernicious attacks of malaria in northern latitudes occur in the summer and autumn and are rare, while in the tropics they occur throughout the year and are very common. The most pernicious attacks occur in patients who have suffered repeatedly from malarial paroxysms which have not been properly treated, and the pernicious symptoms often develop during such a paroxysm. The causes of the pernicious symptoms are not very clearly understood. Bastianelli and Bignami considered that the chief causes for the development of the pernicious symptoms rest in the localization of the parasites in the brain or in other important organs, and also in the number of parasites present. While these reasons undoubtedly have much to do with the development of pernicious symptoms, it is probable that the amount of toxins secreted by the parasites have much to do with the development of these symptoms, as well as the physical condition of the infected individual and his surroundings as regards climate, food, hardships, etc.

The pernicious forms of malaria may be classified in two ways, *i. e.*, from the character of the temperature curve, and from the most prominent symptoms which are present. Under the first classification we may have *tertian*, *quartan*, *remittent*, or *larral* pernicious malaria. Under the second classification we may have *comatose*, *delirious*, *tetanic*, *clamptic*, *hemiplegic*, *dysenteric*, *choleraic*, *algid*, *cardialgic*, *hemorrhagic*, *pneumonic*, and *bilious* pernicious malaria fevers. Only a few of the most common varieties will be described; these are not disease entities, but only take their name from the clinical symptoms which are present.

The Comatose Form.—This is the most frequent form of pernicious malarial fever and occurs in two ways, either as a sudden attack of coma or a gradually developing comatose condition during a paroxysm of fever. The sudden development of coma is rare and, unless at once recognized and treated, invariably fatal. In this form the patient, who may have suffered from repeated attacks of malaria and who has not felt well for some time, is suddenly stricken with profound coma, falls to the ground, and, in the fatal cases, does not again regain consciousness. This form is apt to be mistaken for apoplexy. The face is suffused, the pupils contracted, the pulse at first full and bounding, later soft, rapid, and thready, the respirations hurried and sometimes stertorous. The temperature is irregular, seldom reaching 103° F., and is often subnormal. Death generally occurs within two days. The most common form is that in which coma develops more or less gradually during an attack of the fever. The symptomatology of the attack is the same as in the ordinary paroxysm, but the nervous symptoms such as restlessness and delirium may be more marked. As a rule, the patient is restless and mentally depressed. Following this there develops a tendency to somnolence, which deepens into stupor and finally coma. Unconsciousness is complete, the patient lying perfectly quiet, or there may be restless movements of the arms and legs. The skin is often somewhat icteric in hue, and hot and dry; the pupils are generally equally contracted, but may be unequal or equally dilated. The icteric hue, which is often present in the

conjunctivæ, has led to a diagnosis of yellow fever in infected regions. The face may be cyanotic but in old infections it is generally pale. Slight spasms of the muscles of the face are not infrequent. The tongue is tremulous, dry, and thickly coated, and slight hemorrhages into the skin are sometimes observed. There may be hemiplegia present or total paralysis. The respirations are slow and quiet, but may be irregular, rapid, and stertorous. The pulse is generally slow and full and incompressible at first, but becomes rapid and weak as the paroxysm progresses. The feces and urine are passed involuntarily, and retention of urine may occur. In cases having a fatal termination the pulse becomes thready, rapid, and intermittent; the respirations irregular, labored, or shallow; the skin pale and bedewed with cold perspiration, and death occurs by collapse. In cases which recover, the temperature falls, accompanied by perspiration, the consciousness is slowly regained, but in many of these cases the improvement is only apparent and the patient relapses in the course of a few hours into a second paroxysm, and perhaps into a third, which usually results fatally. Between the paroxysms the mental condition is one of torpor or great mental depression accompanied by severe headache. The duration of the coma is variable, lasting from a few hours to three or four days, but it generally does not persist longer than twenty-four to twenty-six hours.

The temperature course in this form is irregular. Some cases present high temperature throughout, between 103° and 104° F., while in others the temperature may remain slightly above normal, or even below normal. In fatal cases the fever if present, declines, as a rule, some hours before death, but it may ascend. Manson cites temperatures of 101° and 112° F. In a fatal case observed by the writer the temperature never went above 101° F. until a few hours before death, when it rose to 103°, the entire attack lasting six days.

Besides the comatose form there are other cerebral forms, among which may be mentioned the *delirious* form in which the patient has hallucinations, followed by violent excitement; the *eclamptic* form, which is common in children, in which the symptoms are similar to those of cerebrospinal meningitis, there being vomiting, fever, headache, pain in the back of the neck, convulsions, and coma; the *hemiplegic* form characterized by hemiplegia; and the *amaurotic* form, in which complete blindness may result.

The Algid Form.—In certain regions of the Southern and Middle States, as well as in other localities, there occur pernicious forms of malaria known as algid forms. The symptoms develop after one or more paroxysms, or they may be the primary symptoms. The characteristic condition is one of profound collapse attended by profuse perspiration, the temperature at the same time being more or less elevated, although in many cases it is subnormal. Patients suffering from this form of malarial infection present a characteristic countenance, the cheeks being drawn and pinched, the eyes sunken, the nostrils dilated, and the skin bedewed with perspiration. The entire body is cold and the skin cyanotic and bathed with cold sweat. The lips and finger nails are intensely cyanotic. The tongue is tremulous, dry, and coated with a dirty white fur. The

pulse is rapid, thready, and easily compressible, and generally more or less intermittent; the heart-sounds are muffled and the second sound sometimes inaudible, and as death approaches the pulse becomes imperceptible; the respirations are irregular, superficial in character, and labored; the muscular weakness is extreme, while the mental condition is one of apathy and indifference. These symptoms rarely last over a few hours, death generally resulting. This is one of the most pernicious types of malarial infection and one which is most resistant to treatment.

The Choleraic Form.—In certain cases the patient presents symptoms which very closely simulate those of cholera. Diarrhœa is by no means an infrequent symptom in estivo-autumnal fever, but in these cases choleraic symptoms develop, the stools suddenly becoming watery, very profuse, and numerous. The diarrhœa leads to profound collapse accompanied by the usual symptoms. Death is a common result in untreated cases, but where therapeutic measures are applied promptly, recovery occurs in the majority. The temperature is generally elevated. The great importance of this variety consists in the liability with which it may be mistaken for cholera in countries in which cholera occurs.

Closely allied to the choleraic form, so far as symptoms pointing to the abdomen are concerned, is the *gastralgic* form which has been described by Laveran, Colin, and Haspel. Prominent symptoms are agonizing pain in the epigastrium, the vomiting of matter tinged with blood, while a diarrhœa severe in character may also occur at the same time. This form is interesting from a surgical standpoint, as a diagnosis of appendicitis may be made.

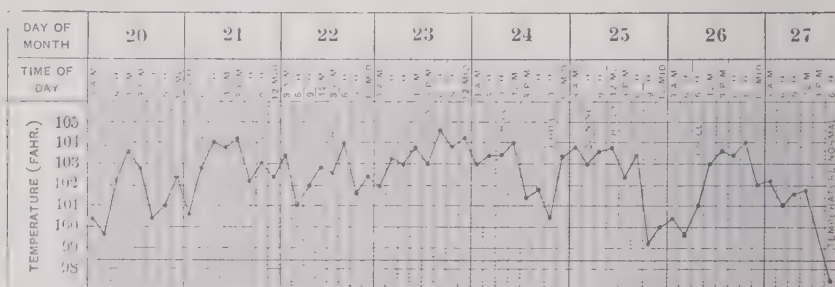
The Dysenteric Form.—A considerable proportion of patients suffering from estivo-autumnal infection present symptoms of dysentery, consisting in frequent mucoid and bloody stools, tenesmus, colicky pain in the abdomen, progressive emaciation, etc. Dysenteric symptoms in the tropics are often due to malarial infection, and probably a certain proportion of cases diagnosed as dysentery in tropical regions are in reality the dysenteric form of malarial infection.

The Bilious Form.—Certain cases of malarial infection present a symptom complex in which jaundice and the vomiting of bile-stained fluid are most prominent. These cases have long been known under the term of "bilious remittent fever." The attack is generally characterized in the beginning by well-marked malarial paroxysms, but the temperature becomes more or less remittent or continuous. Marked jaundice appears and severe vomiting is present, the matter vomited being greatly bile-stained. Epistaxis is rather common, and hematemesis often occurs. Delirium may be present or there may be a condition of semicoma, or even coma. The patient often complains of severe pain in the epigastrium, and hiccough is one of the most common symptoms. The temperature curve in well-marked cases is generally remittent or almost continuous, somewhat resembling that of typhoid fever. If untreated, this form of the disease is almost invariably fatal, but if the proper therapeutic measures are applied recovery is generally the result.

The Irregular and Remittent Forms.—Any of the malarial infections may become irregular or remittent in character as regards the temperature, but the estivo-autumnal infections are especially prone to present irregularities in the fever, which in many cases are very confusing. A malarial fever may become continuous, irregular or remittent in various ways, the principal of which are the anticipation or retardation of the paroxysm, infection with one or more groups of parasites, and insufficient treatment by quinine. In these infections it is very seldom possible to demonstrate the complete life cycle of the parasite in the blood, but in those cases which are caused by mixed infection with more than one variety of parasite the forms may be easily differentiated. It is these forms, especially the remittent or continuous types, which are so often confused with typhoid fever and septicemia, especially where estivo-autumnal infections are infrequent.

The remittent type is the one which is of the most importance, as cases of this kind are not infrequently supposed to be typhoidal in character. The symptoms are very variable and inconstant. The prodromal

FIG. 5



Subcontinued estivo-autumnal malarial fever.

symptoms are generally weakness, malaise, more or less headache, loss of appetite, etc. The attack may or may not begin with chills, but there are always slight chilly sensations. The patient's appearance is very suggestive of typhoid, the face being flushed, the eyes brilliant, the mucous membranes congested, and the skin hot and dry. There is severe headache and muscular pain, especially marked in the back and limbs. There is often marked nervousness, sleep being poor, and there may be slight delirium. The tongue is dry and coated, while nausea and vomiting are present and diarrhea is common. The pulse is rapid and dicrotic in character, while the respirations are hurried and often very superficial. There is often tenderness of the abdomen, and the spleen is generally more or less enlarged. In some cases the resemblance to typhoid is very remarkable, epistaxis, an eruption resembling the roseola of that disease, and tenderness and gurgling in the right iliac region being present.

The temperature curve in these infections is very variable, but usually there are present more or less marked intermissions, thus serving to differentiate it from the fever of typhoid. In rare cases, however, the

curve cannot be distinguished from that of typhoid fever, there being slight daily remissions but no marked intermissions.

An examination of the blood, if carefully made and repeated if necessary, will invariably demonstrate the type of malarial parasite concerned, which is generally one of the estivo-autumnal organisms. If properly treated, the symptoms are easily controlled within a week, although in very rare instances the parasites may be very resistant to quinine and persist for eight to ten days.

Combined Infections.—Any of the varieties of malarial plasmodia may occur together, thus causing what is known as a combined infection. In such infections the temperature chart is apt to be irregular or remittent, but very often one type of parasite may so predominate in numbers that it will give to the infection the characteristic symptoms caused by the particular organism concerned; thus we may have a combined infection with estivo-autumnal and tertian parasites in which the former are so much more numerous that the case presents the symptoms of an estivo-autumnal infection.

Latent and Masked Infections.—In previous communications¹ the writer has called attention to the importance of the occurrence of latent and masked malarial infections, especially in individuals who have resided in malarious localities. A latent malarial infection may be defined as one in which parasites can be demonstrated in the blood but in which there are no symptoms which would lead a clinician to suspect malaria, while a masked infection is one in which the symptoms are obscured by those of some accompanying disease, or in which they are atypical in character. At the U. S. Army General Hospital in San Francisco, California, out of 1267 cases of malaria in which the parasites were demonstrated in the blood, 395, or 25 per cent., showed either latent or masked infections. The estivo-autumnal infections comprised 275 of the cases, thus showing that this parasite is concerned most often in latent and masked malaria. Examinations of the blood in such cases have shown the parasites in all stages of development, but always in small numbers. Of the 395 cases, 277 were latent infections, or infections in which the malarial parasites could be demonstrated in the blood but which presented no clinical symptoms, while 118 were masked infections, most of them being in patients suffering from other diseases which masked the malarial symptoms. Of the masked infections, chronic dysentery, chronic diarrhoea, pulmonary tuberculosis, and amœbic dysentery were the diseases which most often masked the malarial infection. Lobar pneumonia was simulated very closely in three cases by the malarial infection.

The remarkable percentage of latent and masked infections, as shown in the cases studied at this hospital, proves the great importance of a routine examination of the blood in all patients coming from malarious localities. It is obvious that recognition of such infection is of the greatest importance, as in the latent infections we are thus able to cure the disease before any annoying symptoms are present, and in the masked cases

¹ *Medical Record*, February 15, 1902, also *American Medicine*, October 21, 1904. *The Malarial Fevers, Hemoglobinuric Fever, and the Blood Protozoa of Man*, New York, 1909, p. 228.

we are able to remove the malarial element which may be of the greatest importance as regards recovery. Not only is this so, but an examination of the blood in these cases will often prove of service, not only to the physician, but also to the surgeon, as certain malarial infections simulate very closely surgical conditions, especially appendicitis.

Complications.—The conditions complicating malarial infection should not be confused with the infection itself; in other words, a typhoid fever complicating malaria should not be considered as being due to malarial infection; nor is a pneumonia which may complicate such infections due to the malarial parasites. Of the many diseases which may complicate the various forms of malaria, and especially the estivo-autumnal infections, the following may be mentioned:

Of the diseases of the *nervous* system, acute mania, severe hysteria, paraplegia, hemiplegia, and meningitis may be noted.

The most serious diseases of the *respiratory* system complicating malarial infections are lobar and lobular pneumonia. For a long time pneumonia complicating these fevers was held to be due to the malarial plasmodia, and while this is true in a very small number of cases, true lobar or lobular pneumonia may occur coincidently with any of the malarial fevers. Pneumonia may complicate the malarial infection at any time, and may develop suddenly or insidiously. The course of the disease is similar to that in a patient in whom no malarial infection is present, but the prognosis in pneumonias complicating the estivo-autumnal infections is very grave, Ascoli placing the mortality as high as 60 to 78 per cent. The pneumonic symptoms may mask the malaria, or *vice versa*. Acute bronchitis is very common in all varieties of malarial infection and in the estivo-autumnal infections is observed in about 40 per cent. of the cases. Tuberculosis very often occurs in conjunction with malarial infections, and often the symptoms of the disease mask those of malaria. Pleurisy is somewhat rare.

Diseases of the *circulatory* system not infrequently complicate malarial fevers. Many cases of malaria present organic disease of the heart and in such cases the prognosis is often grave. Acute endocarditis is rare while functional disorders of the heart are very common.

The most common disease of the *genito-urinary* system complicating malaria is nephritis. It is more frequently a sequel than a complication. Orchitis and epididymitis very commonly occur as complication, but a history of gonorrhœa can usually be obtained. It is doubtful if true malarial orchitis ever occurs.

The most frequent and important disease of the *gastro-intestinal* tract complicating the malarial fevers is dysentery or some form of enteritis. Dysentery is especially frequent in patients returning from regions where both malaria and dysentery are endemic. Dysentery complicating malaria is very apt to run an aggravated course, and the prognosis is much worse than when it occurs alone.

The administration of quinine in cases complicated by dysentery has always resulted in the removal of the malarial infection and the improvement of the dysenteric condition. In a certain proportion of patients suffering from dysentery, the disease is probably due to the localization of the malarial parasites within the capillaries of the intestines, for in no

other way can we explain the rapid recovery of many such patients after the administration of quinine.

Typhoid fever occasionally occurs in conjunction with the malarial fevers. In nearly 5000 cases of malaria personally observed the complication of the disease with typhoid has only occurred 10 times. Of these 10 cases, 6 were combined infections of typhoid and estivo-autumnal malaria, 3 combined infection with tertian malaria, and 1 with quartan. As a rule, the malarial attack occurs during convalescence from typhoid but may occur during any stage of the disease. When malaria is complicated by typhoid, or even *vice versa*, the symptoms do not vary markedly from those occurring in a single infection.

The discovery of such combined infections is of the greatest importance, as the malarial element in the case can be easily removed by the proper administration of quinine.

Among other complications may be mentioned erysipelas, rheumatic fever, sciatica, various skin eruptions, and variola.

Sequelæ.—The most common are those occurring in the *nervous system*, the *genito-urinary system*, the *glandular system*, and the *blood*.

The most numerous complications occur in the nervous system, due to the blocking of the capillaries of the cortex of the brain by the malarial parasites and their products, or to the effect of certain toxins liberated by them. Local paralysis frequently occurs, due undoubtedly to the blocking of the capillaries of certain cortical regions, but these are generally evanescent in character. Various psychical disturbances are common and the memory is often defective after repeated malarial attacks. Melancholia, delusional insanity, and mania may follow severe attacks of estivo-autumnal malaria, and especially common is a condition of melancholia. Mania, melancholia, and delusional insanity have been observed in soldiers returning from the tropics which were undoubtedly sequelæ of severe and repeated attacks of estivo-autumnal malaria. Multiple neuritis rarely occurs. One of the most common sequelæ is neuralgia, but it should be remembered that many so-called malarial neuralgias have no connection whatever with malarial infection.

Among diseases of the genito-urinary system, albuminuria is of frequent occurrence during acute attacks of malaria and oftentimes persists for some time after the cessation of such attacks. Thayer found that albuminuria was most frequent in estivo-autumnal infections, occurring in 58.3 per cent. of these infections, in contrast to 38.6 per cent. of tertian and quartan infections. From personal experience, albuminuria apparently occurs in about 65 per cent. of cases of estivo-autumnal and in about 30 to 35 per cent. of cases of tertian and quartan malaria.

Both acute and chronic *nephritis* may occur as sequelæ of the malarial fevers. It may be stated that all forms may occur, the most common being acute glomerular and chronic parenchymatous and interstitial nephritis. Personal observations suggest that nephritis occurs in at least 4 per cent. of all cases of estivo-autumnal infections, the most common form being chronic parenchymatous. It is rare in tertian and quartan infections, but is always found in fatal cases. Polyuria is a frequent sequela of the malarial fevers, especially the estivo-autumnal variety,

but, as a rule, the condition is transient, although it may be persistent. Glycosuria is a rare sequel.

Among the sequelæ in the glandular system may be mentioned hypertrophy of the liver and rupture of the spleen. After repeated attacks of malaria, a condition which may be termed hypertrophic, malarial hepatitis, may develop, the liver becoming greatly enlarged, while the perilobular tissue is increased in amount and the capillaries greatly dilated and congested. The condition does not, as a rule, cause any clinical symptoms. Many authorities have endeavored to prove that continued malarial infection will give rise to cirrhosis of the liver, but when present it is undoubtedly due to some other cause, as cirrhosis of the liver is no more common in malarial than in non-malarial districts.

Rupture of the spleen is a rare sequel of malaria and is generally due to falls or blows, by which the greatly enlarged organ, rendered soft and pliable by the malarial infection, is ruptured. The writer has reported two cases of this character. The symptoms are sharp, lancinating pain in the left side and the usual symptoms of collapse due to hemorrhage. Death may occur in a few moments or after a day or more.

The Blood.—In repeated and severe attacks of estivo-autumnal malaria a post-malarial anemia is produced which may be very severe and persistent. In tertian and quartan infections, after complete recovery, the regeneration of the red-blood corpuscles is generally rapid, but in the estivo-autumnal infections the anemia may persist. There is a marked reduction in the hemoglobin, always in about the same ratio as the red-blood corpuscles, while the leukocytes are reduced in number as a whole, but the large mononuclear forms increased.

A pernicious type of anemia, occurring as a sequel of the estivo-autumnal infections, have been observed by the writer in 6 cases, all of which proved fatal. The blood showed no nucleated red cells, the red cells numbering from 490,000 to 590,000 per cmm. The leukocytes were about normal in number, relatively, but the polymorphonuclear leukocytes were increased. Poikilocytosis was not marked, but there were great differences in the size of the red cells. This form of severe anemia has been described by Bignami and Bastianelli, and is remarkable in that no nucleated red cells can be demonstrated, due, according to these authors, to the almost complete absence of regenerative power in the blood-forming organs. In certain instances the classical type of pernicious anemia may occur as a sequel especially of the estivo-autumnal variety.

Malarial Cachexia.—In patients who have suffered from repeated attacks of malarial fever which have not been properly treated, a peculiar condition develops, the most characteristic symptoms of which are a more or less severe anemia and a greatly enlarged spleen. This so-called malarial cachexia is most frequent in tropical regions in which the estivo-autumnal infections are endemic, and least frequent in localities in which tertian infections are present. It is especially apt to develop after latent and masked infections which have gone untreated. The anemia partakes of the character of a secondary anemia, the red cells being reduced to 2,000,000 or less per cmm. while there is a marked

increase in the large mononuclear leukocytes and a corresponding decrease in the hemoglobin. The spleen may be enormously enlarged, reaching as low as the crest of the ilium, but as a rule it does not extend more than 4 to 8 cm. below the border of the ribs. It is firm and not painful on palpation.

Patients suffering from malarial cachexia present a peculiar yellowish or grayish hue of the skin, while the mucous membranes are very pale, due to the anemia. There is a loss of appetite, diarrhœa, dyspnœa, emaciation, and a general condition of nervous exhaustion. The temperature may be normal, but generally shows a slight rise toward evening; it seldom reaches 102° F. The condition is especially frequent in children living in tropical localities.

The long-continued malarial infection renders these patients especially liable to acute infectious diseases, and slight injuries are often attended by serious results, such as phlegmonous inflammation or hemorrhage. Marchiafava and Bignami state that it has never been their experience to observe in patients suffering from malarial cachexia, grave infections with many parasites in the blood, but that there are always a few parasites and very little melanemia. Malarial cachexia cannot always be determined by microscopic examination of the blood, as the parasites will not be present in any number except when there are acute symptoms, and even melanemia may be almost absent.

Latency and Recurrence.—Examinations of the blood of persons residing in malarial localities often show the presence of the parasites although no symptoms of the disease are present. In such instances the infection is said to be latent. It is also well known that most cases of malaria improperly treated relapse sooner or later, and during the period between the relapses the disease is also latent. Of 1297 cases of malaria in Americans returning from the Philippines studied by the writer, no less than 307, or nearly 24 per cent., were latent infections, and in the Philippines of 225 Filipinos, apparently in good health, 115, or 51 per cent., showed a latent malarial infection. The subject of *recurrence* is of great importance and much work has been done upon its etiology. If physicians properly treated their malarial patients recurrences would be comparatively rare, and the danger of patients becoming malarial carriers would be practically obviated. Recurrences are undoubtedly due to a certain number of plasmodia escaping the effects of quinine, and living in some form in the body until conditions are favorable for their rapid multiplication, when a relapse results. The time of recurrence varies in the different infections. In 55 cases of tertian estivo-autumnal infection observed personally the time of recurrence varied from ten to eighty days; the greatest number of relapses occurred between the twentieth and thirtieth days, namely, 23, and almost as many between the thirtieth and fortieth days, namely, 16. In most instances secondary relapses occurred at longer intervals than the primary relapse. Of 18 tertian cases in which relapse occurred, the shortest period of relapse was sixteen days, and the longest was forty-one days; most of the cases relapsed between the fifteenth and thirtieth days.

The exact cause of latency and recurrence is still unknown. There

are three theories suggested. The theory of Ross is that the plasmodia are always present and undergo their normal schizogony, but in such small numbers that no symptoms are produced during the period of latency, and that relapse is due to rapid multiplication brought about by favorable conditions. The theory of Schaudinn is that relapse is due to parthenogenesis of the *macrogamete*. The theory of the writer is that latency is produced by the intracorpuseular conjugation of the young *schizonts*, leading to the production of a resting form, which, when conditions are favorable, undergoes multiplication, and a relapse occurs. There is evidence in favor of all these theories, but no one of them can be said to be generally accepted. It is quite probable that the theory of Ross is correct as regards short-term relapses, but it is certainly most reasonable to believe that some resting form of the plasmodia must exist to explain relapses occurring after several months, the so-called "long-term" relapses. Bignami has recently stated that he believes relapses are due to the sporulation of quinine-fast strains of malarial plasmodia.

Diagnosis.—From clinical symptoms alone this is often difficult and sometimes impossible, especially in the estivo-autumnal infections, but there are two methods which are all-sufficient and deserving of confidence, *i. e.*, examination of the blood and the therapeutic test by quinine. Of these two methods the examination of the blood is the more valuable, for the therapeutic test may be misleading, as other fevers may decline under the administration of this drug. The mild tertian and quartan infections, if uncomplicated, can usually be easily diagnosed by the clinical symptoms alone, but when double infections occur, a diagnosis of malaria is often impossible from a clinical study of the symptoms, and in estivo-autumnal infections a diagnosis of malaria is generally impossible without an examination of the blood.

Examination of the Blood.—In most instances one examination is sufficient, but if a negative result is obtained repeated examinations should be made at short intervals. If this is done, almost invariably, even in the most obscure estivo-autumnal infections, the parasites will be discovered. Cases of malaria of this variety undoubtedly occur in which no parasites can be demonstrated in the peripheral blood, but not when the infection is severe enough to produce symptoms. The symptoms in estivo-autumnal infections are often so obscure, or even so slight, that malaria is not suspected, and in many cases an examination of the blood will show the presence of the malarial plasmodia before any clinical symptoms sufficiently severe to excite a suspicion that the infection existed. An examination of the blood in all cases of disease occurring in malarious localities should be a routine measure.

The blood may be examined either in the fresh state or in stained specimens. The desirability of the examination in the fresh condition rather than in permanent specimens, which have been hardened and stained, has been advised, but since the development of Wright's modification of Romanowsky's stain, the examination of specimens stained by this method is preferable, except in the hand of an expert, to the examination of the fresh blood. For the examination of certain stages in the

life cycle of the malarial plasmodia, the examination of fresh blood is essential, but with improved methods of staining, better results will be arrived at by the majority of physicians if stained specimens are used.

Examination of Stained Specimens.—There have been numerous methods proposed for the staining of the malarial plasmodia, the most valuable of which have been Romanowsky's and its many modifications, such as Jenner's and Wright's. Probably the most satisfactory is the modification of Romanowsky's stain described by Wright. While the method of preparing the staining solution is somewhat complicated, a careful following of the directions will result satisfactorily. Numerous commercial houses have Wright's stain for sale, but, as a rule, the stains purchased in this way are unsatisfactory and cannot be relied upon. It is much better for the physician to make his own stain. Dr. H. R. Oliver has recently modified Wright's method slightly, and the staining solution as prepared by him gives very excellent results. The following is the method of preparation:

Preparation of Wright's Stain.—In a flask add 0.5 gm. of S. P. bicarbonate of soda to 100 cc. of distilled water, dissolve thoroughly, and slowly add, while shaking, 1 gm. of methylene blue (Grubler's); heat for one hour in an Arnold sterilizer after the steam is up and then cool the solution. Make a solution of yellow aqueous eosin (Grubler's) by adding 1 gm. of the eosin to 1000 cc. of distilled water, and add this, while stirring, to the cooled methylene blue solution until a well-marked precipitate appears and the surface of the mixture is covered with a greenish metallic scum. Test by placing a drop of the mixture upon filter paper; when sufficient eosin solution has been added a well-marked pink halo should surround the small amount of violet precipitate upon the paper. Allow the mixture to stand for about ten minutes and then filter it through one small filter paper; after filtration is complete remove the paper from the filter, unfold it so that it is half folded, and press between several thicknesses of blotting paper; remove the upper half of the paper, when all of the precipitate will be found upon the lower half. The precipitate is carefully removed from this portion of the paper, placed in a glass dish, and dried in a hot-air oven at 60° C.; it is then crushed into a powder which is used in preparing the staining solution as follows:

Take 0.3 gm. of the powder and dissolve it in 100 cc. of methylic alcohol (Merck's reagent), filter, and bring the filtrate up to the original 100 cc. by adding the requisite amount of methylic alcohol. The staining solution is now ready for use and will keep well for months.

Method of Using.—Add a few drops of the staining solution to the blood smear and let stand for from three to five minutes; this fixes the specimen. Then add enough distilled water to the preparation to cause a metallic scum to appear upon the surface; let stand for from three to five minutes; wash in distilled water; examine directly when dry or mount in neutral balsam. The washing with distilled water is very important, as it removes the precipitate which is generally formed during the staining process, and differentiates the chromatin of the nucleus of the parasites.

By this method all varieties of malarial parasites stain as follows: The protoplasm stains a robin's-egg blue, the vesicular portion of the

nucleus remains unstained, while the chromatin stains a dark cherry red. The very young forms of the plasmodia—that is, the ring forms—are very distinctive, appearing as a bright blue ring, at some portion of which is situated a dark cherry red dot marking the chromatin of the nucleus, the red cell being stained a light red or brownish yellow.

The only objection to the use of staining methods is that certain other material, especially broken-down leukocytes or extraneous matter, may take the stain and be so situated within the red cells as to be mistaken for the organism. But to one who has once seen preparations stained by the method described, no such mistake is possible.

Differentiation in Stained Preparations.—The malarial plasmodia may be easily differentiated in stained preparations if certain morphological peculiarities of the several species be remembered. The following points are useful in differentiating the various species:

Plasmodium Vivax.—(Tertian Plasmodium).—(1) Large size, after the development of pigment. (2) Number of *merozoites*, 12 to 24, arranged irregularly. (3) Presence of all stages in the peripheral blood. (4) Increased size of the infected erythrocyte. (5) Presence of Schuffner's "dots" (eosinophilic granules) in the infected erythrocytes.

Plasmodium Malariae.—(The Quartan Plasmodium).—(1) Medium size, after the development of pigment. (2) Number of *merozoites*, 6 to 12, and regular arrangement of the same. (3) Presence of all stages in the peripheral blood. (4) No enlargement of the infected erythrocyte. (5) Absence of Schuffner's "dots" in the infected erythrocyte.

Plasmodium Falciparum.—(Tertian Estivo-autumnal Plasmodium).—(1) Small size, even when fully developed. (2) Number of *merozoites*, 10 to 15, as a rule, small and arranged irregularly. (3) Only "ring forms" and young pigmented forms occur in the peripheral blood, as a rule, together with crescents (*gametes*) after the infection has persisted for several days. (4) Infected erythrocyte generally smaller than the normal erythrocytes. (5) Presence of Maurer's "dots" or basophilic granules. (6) Crescentic shape of the *gametes*.

Plasmodium falciparum quotidianum, the quotidian estivo-autumnal plasmodium, differs from *Plasmodium falciparum* in being much smaller at every stage in its development, while the *merozoites* vary in number from 6 to 18, the average being from 12 to 14. The "ring forms" are very minute, resembling in this respect the *piroplasma*.

The Therapeutic Test.—As Osler has well said, any fever which resists the action of quinine properly administered for more than four or five days is not malarial in character. This fact is used as a means of diagnosis when for any reason an examination of the blood is impossible, but it must not be forgotten that quinine is capable of reducing the temperature in diseases other than malaria. In many instances, also, much harm may be done, especially in typhoid fever, which often resembles the continued estivo-autumnal infections, and in which quinine may be harmful.

Differential Diagnosis of the Various Forms of Malarial Fever.—A differential diagnosis of the various types of malaria is most quickly and scientifically made by an examination of the blood. In this way the

entire life cycle of the tertian and quartan plasmodia may be studied, and the various types of plasmodia easily differentiated. When, however, an examination of the blood for any reason is impracticable, the clinical symptoms may be of service in distinguishing the various types; thus, a typical tertian or quartan infection is easily differentiated by the time of the occurrence of the paroxysm and the study of the temperature chart alone, but it is impossible to differentiate a double tertian infection from a quotidian estivo-autumnal infection in this way, and it is obvious that mixed infections cannot be differentiated by the clinical symptoms only. The temperature chart occurring in uncomplicated cases of tertian estivo-autumnal fever is so characteristic that a differentiation of this form from other malarial infections can be easily made, but in all forms of malarial infections, the diagnosis should rest chiefly upon the result of blood examinations. While it may not appear to be of great importance to be always able to differentiate the exact type of malarial infection that is present, it surely is so from a scientific standpoint, and is often so practically. Grave mistakes have been made in considering a severe estivo-autumnal infection as a mild tertian.

While in uncomplicated tertian and quartan malaria the examination of the blood may not be absolutely essential in making a diagnosis, it is in the estivo-autumnal infections, and especially in those presenting anomalous symptoms, that such an examination is of the greatest service. In these cases the presence in the blood of the small intracellular ring forms, or of the crescents, demonstrates at once the infection.

The differential diagnosis of the malarial fevers from other disease processes which may closely resemble them is only possible, in many instances, by the use of the microscope. This is especially true of the estivo-autumnal infections which so often present anomalous symptoms resembling those of some other disease, that from a study of the clinical symptoms alone a diagnosis cannot be arrived at. There are a number of diseases with which malarial fevers may be confused.

Typhoid Fever.—Perhaps no other disease has been so often confused with malaria as has typhoid fever. This was well borne out during our war with Spain. Clinically, the confusion regarding these two diseases has much to justify it. It is probable that a typical tertian or quartan infection is never suspected to be typhoid, or *vice versa*, but in the more irregular estivo-autumnal infections this mistake has often been made. In regions in which estivo-autumnal malaria is endemic, or supposed to be, it is a very common mistake to regard patients suffering from typhoid fever as victims of this type of malaria. This is because many cases of estivo-autumnal infection present typhoid symptoms and a clinical differentiation is impossible. The mistake of considering a typhoid infection, however, as malarial, after quinine has been administered for several days, is inexcusable, for experience has shown that there is no malarial fever which will resist the action of quinine, when properly administered, for a period of six to eight days. If parasites are present in the blood, and the Widal test and blood cultures are negative, the diagnosis is at once established, and cases of combined infection are rare. During the decline of the temperature in typhoid cases a marked

intermittent temperature may be observed which resembles very closely that of quotidian malarial infection. Chills also may occur at this time and a diagnosis of malaria is made. Unless supported by the finding of the malarial plasmodia in the blood, such a diagnosis is unjustifiable.

Yellow Fever.—In regions in which yellow fever is endemic, the differentiation of malaria from this disease is often exceedingly difficult unless a blood examination be made. The so-called "bilious remittent type" of estivo-autumnal malaria is especially apt to simulate yellow fever, there being present a yellow tint of the skin, severe vomiting, sometimes of dark material resembling "black vomit," while albumin appears in the urine. A patient presenting such a clinical picture in a yellow fever region is almost always thought to have yellow fever, and it is in these cases that an examination of the blood is of the greatest importance.

Tuberculosis.—In many cases tuberculosis is complicated by a streptococcus infection, and the temperature chart closely resembles that found in quotidian malarial infections. There may also be daily chills, or chilly sensations, and the patient presents the facies so often observed in long-continued malarial infection. An examination of the sputum will generally result in the demonstration of the tubercle bacillus, while physical examination will show pulmonary lesions to be present. An examination of the blood, however, is essential, as not infrequently patients suffering from tuberculosis contract malaria.

Hepatic Abscess.—In regions where amœbic dysentery is endemic, certain cases suffering from hepatic abscess may present symptoms which closely simulate those of malarial fever; thus there may be daily chills and a temperature curve, which, while it is that of sepsis, very closely simulates that of some of the forms of estivo-autumnal infection. The chief clinical points in favor of hepatic abscess are enlargement of the liver and tenderness over the hepatic region, while the spleen is not enlarged. A history of dysentery can generally be obtained in cases of hepatic abscess. Examination of the blood will decide if malaria be present, while a leukocytosis will point toward a hepatic abscess.

Ulcerative Endocarditis.—The temperature chart in ulcerative endocarditis often resembles that of quotidian malaria. Examination of the heart will generally suffice to determine the nature of such cases, and if not, an examination of the blood will decide the question.

Cerebral Apoplexy.—The differential diagnosis between the comatose pernicious form of malaria and cerebral apoplexy is often extremely difficult unless a blood examination be made. The main clinical points in arriving at a diagnosis of malaria are high fever, although this is not constant, the age of the patient, and the splenic enlargement. An examination of the blood will generally decide the question at once.

Sunstroke.—Especially in tropical or subtropical regions, certain forms of pernicious malaria very closely resemble sunstroke. It should be remembered that in such regions the heat very often aggravates or brings on severe malarial paroxysms. It is therefore necessary to be sure in such cases whether or not a malarial infection be present and a microscopic examination of the blood is often our only means of arriving at a differential diagnosis.

Dysentery.—Malarial infections may occur with dysentery, and as malarial infection is capable of producing the clinical symptoms of dysentery, it is important that a differential diagnosis should be arrived at in regions where dysentery is endemic. An examination of the blood is therefore essential in every case of dysentery occurring in such regions.

Among other disease processes which may be confused with malaria may be mentioned septicemia, pyemia, diseases of the gall-bladder or ducts, acute suppurative processes in any of the viscera, pneumonia, and Weil's disease. In all of these a careful examination of the blood is sometimes our only method of arriving at a differential diagnosis.

Prognosis.—While the prognosis in uncomplicated cases of tertian and quartan malaria is good, fatal cases of both of these forms of fever have occurred, especially the quartan variety. As regards the prognosis of the estivo-autumnal infections, certain factors have to be taken into consideration, such as locality, age, occupation, position in life, and physical condition. These apply with some force also to the prognosis of the simple intermittent fevers, but are especially important in the estivo-autumnal infections.

In the tropics the prognosis in estivo-autumnal infections is much more grave than in temperate regions, and in certain local regions these fevers are much more fatal than in others. The prognosis is most grave at the extremes of life. It is more grave in the poor than in those who are well-to-do, in the case of individuals in ill health than in those who are well-nourished and healthy. Complications also have much to do with the prognosis, among the most serious being the various forms of nephritis, tuberculosis, pneumonia, dysentery, and the infectious fevers. The prognosis in the pernicious varieties of estivo-autumnal infection should always be guarded, especially if the patient is seen after having suffered from several severe paroxysms, although even then if treatment be vigorously instituted the patient may recover. However, the pernicious symptoms may last for several days, and despite all treatment, death ensue. The prognosis is very grave in the cerebral forms, especially the comatose form. In the algid form the prognosis is almost as grave as in the cerebral forms, and not a few go on to a fatal termination despite all treatment. The prognosis is very grave in the choleraic form and also the pneumonic. In the dysenteric form the prognosis is always grave, depending upon the fact that the dysenteric symptoms have often masked those of malaria for a considerable time and treatment is not instituted until too late.

In soldiers campaigning in tropical countries where pernicious forms of malaria are endemic, many deaths are often due to this cause, and the prognosis in such infections should also be very guarded.

In malarial cachexia when a change of locality cannot be secured the prognosis is always grave, death resulting not so much from the malarial infection as from some complicating disease. While under proper treatment a great majority of cases of estivo-autumnal infection recover, unless quinine be administered for a long period of time, relapses invariably occur, and one of these may prove fatal. It may be stated as an axiom that the prognosis in tertian and quartan malaria is good, but in

the estivo-autumnal infections it is always grave, as at any time during their course, pernicious symptoms may develop and prove rapidly fatal.

Prophylaxis. Prophylaxis in malarial disease is of much greater importance at this time than ever before in the history of such infections. We now know the etiological factors and their method of transmission, and that proper methods of prophylaxis have already resulted in the disappearance of the infection from numerous localities.

The discovery of the relation of the mosquito to the transmission of the malarial fevers placed their prophylaxis upon a scientific basis, and much has been accomplished by the destruction of these insects or by protecting man from their bites. If it were possible to either destroy all malaria-carrying mosquitoes, or kill all the plasmodia in the blood of infected individuals, we would succeed in preventing malarial infection in any locality. While either is theoretically possible, we also know that in most instances it is practically impossible, and hence we are forced to combine methods looking both to the destruction of the plasmodia and the mosquitoes.

General Prophylaxis.—General prophylaxis may be considered under the following divisions: (1) Destruction of the mosquito; (2) isolation of the patient; (3) use of quinine; (4) proper treatment of initial infections and of carriers; (5) screening of houses; (6) education of the public.

1. *Destruction of the Mosquito.*—The mosquito is most easily destroyed during the larval stage, and many substances have been experimented with in the hope of obtaining one which would prove efficacious, being at the same time cheap and easily obtained. Sprinkling a thin layer of kerosene upon the surface of the water in which they breed is very efficacious, not only killing the larvæ in the water, but the mosquitoes when in the act of depositing their eggs. The method is especially applicable to collections of water which cannot be drained and which are not very large in extent. The quantity of kerosene used is approximately one ounce to fifteen square feet of surface, and, as a rule, the application does not need to be renewed more than once a month. Collections of water thus treated should be frequently inspected, as the film of oil is apt to be displaced by currents in the water, winds, or by the movements of aquatic animals. This method of prophylaxis should only be depended upon when it is impossible to drain or otherwise destroy the breeding places of mosquitoes.

Of other substances which are capable of killing the larvæ, may be mentioned sulphurous oxide, permanganate of potash with hydrochloric acid, sulphate of iron or copper, carburet of lime, corrosive sublimate, formalin, cresol, certain aniline dyes, and coal-tar. It is obvious that most of these substances cannot be used in practice, the only one really available being kerosene, but this agent cannot be employed in water which is used for drinking purposes unless in the case of large reservoirs where the water is drawn from the bottom.

The introduction of certain fish into reservoirs from which water is used for drinking purposes, and in which mosquitoes breed, has been tried in some localities with success. The fish principally used have been carp and the common stickleback.

The most important of all methods of destroying the mosquito larvæ is by drainage of their breeding places, and this is a method which can be employed over very large areas of country in which malaria is endemic and which experimentally has proved to be of greatest service. In many regions in which the most virulent forms of malarial infection are endemic, drainage is feasible and can be carried out with but little trouble, although the expense is often a factor in the problem, and, as Celli says, "such methods for the destruction of the mosquitoes, while experimentally soluble, will only be practically so when economic interests desire it." Where drainage is impossible the breeding places of the mosquito may be filled up with loam, and it is very important in malarious localities to fill up all areas of depression in the surface of the land that cannot be adequately drained. Swampy areas, if not too large, can thus be filled in, and one of the greatest sources of mosquitoes removed.

A valuable means in conjunction with draining and filling in, is the removal of shelter for the mosquitoes, such as is furnished by jungle, long grass, and vegetation within or along the banks of streams. The removal of the vines which are so often observed enclosing the porches of houses in malarial localities and of the ornamental shrubs with which residential grounds are frequently filled, will result in a great diminution in the number of mosquitoes.

The formation of mosquito brigades, as suggested by Ross, is of the greatest service in limiting malarial infection. This consists essentially in detailing a certain number of men to inspect the premises and destroy the larvæ in the small breeding grounds which harbor the *Anopheles*, such as domestic water receptacles, water butts, and tanks, the removal of small puddles in streets and yards, as well as empty tins, jars, broken bottles, or anything in which water collects, and in which mosquitoes may breed. The region to be covered is divided into portions, each portion being under the supervision of a certain number of men detailed for the purpose. Methods similar to this were pursued in Havana by Gorgas, resulting in the almost total disappearance of the yellow fever mosquito in that city. Garden wells, water barrels, and tanks should be covered, preferably with wire mosquito-netting, containing sixteen meshes to the inch, thus preventing the laying of eggs and the development of the larvæ. If for any reason this is not possible, and the water is not used for drinking purposes, the surface should be sprinkled with kerosene oil.

In the adult stage the mosquito can be destroyed by various odors, fumes, or gases. Among the odors may be mentioned turpentine, menthol, and camphor. Among the fumes, tobacco, chrysanthemum powder, pyrethrum powder, and the fresh leaves of eucalyptus; while among the gases, sulphuric oxide is very efficacious. In using any of these agents it is necessary that the air of the room should be saturated, as otherwise the insect may be simply stunned, and revive when fresh air is admitted. The most useful of these agents is pyrethrum powder, which can be burned in rooms infected with mosquitoes.

2. *Isolation of the Patient.*—It is obvious that if we place the infected individual in a position where the mosquitoes cannot obtain access to him

the transmission of the infection will be impossible. Theoretically, if every patient suffering from malaria could be screened from mosquitoes and properly treated, the disease would entirely disappear, but practically the disease is of such a character that even when no symptoms are present the parasites may be present in the blood and the mosquitoes may become infected. In fact, in estivo-autumnal infections the crescentic form of the organism, which really is the form intended to undergo its life-cycle in the mosquito, is frequently present in the blood when there are no symptoms of malaria, so that it is obvious that we cannot in this way entirely prevent malarial infection. Still the malarial fevers should be regarded as infectious and the patient should be isolated in a screened room. Not only is this of importance to those surrounding the patient, but also to himself, for if he is not protected from mosquitoes he is in constant danger of reinfection from the bites of the insects. Isolation is of the greatest importance in the prophylaxis of malaria, and should be carried out, especially in regions where the more pernicious forms are endemic. Besides isolation of the patient, Ross and Stephens have suggested as a method of general prophylaxis the segregation of certain classes of the population. This applies especially to Europeans living in the tropics. They suggest that the European quarter should not be built in the midst of the native villages in malarious localities, but should be situated at some distance and surrounded by the proper hygienic conditions, which it is often impossible to obtain among a native population.

3. *Use of Quinine.*—The use of quinine as a general prophylactic measure, as suggested by Koch, is undoubtedly of value in malarial regions. If it were administered to all the natives of a malarial region it is probably true that malarial fever would gradually disappear. In other words, the malarial plasmodia present would be destroyed and thus the mosquitoes would not become infected. The method of administering the drug as a prophylactic differs with different observers. It is best given in solution, capsules, or in the form of troches of tannate of quinine made with chocolate. In regions where the tertian and quartan infections occur alone a daily dose of from 3 to 5 grains (0.15 to 0.3 gm.), given in the evening, is sufficient for protection in most instances; but where the estivo-autumnal infections are prevalent, larger doses must be taken. In such regions the administration of 15 grains (1 gm.) of quinine, given upon retiring, every seventh day, will prevent infection in the vast majority of instances. This method the writer used in some of the most malarial regions in the Philippine Islands, with remarkable results, the malarial rate decreasing over two-thirds after a few weeks of such treatment. However, better and quicker results are obtained by the administration of 10 grains (0.65 gm.) upon retiring every third, sixth, and ninth night for two or three weeks after reaching the infected locality, and then using the same amount upon every fifth night thereafter. The continued use of the drug in the doses recommended has been found not to be injurious in the vast majority of instances.

The impression that quinine prophylaxis must extend throughout the year in malarial localities is erroneous, for in almost every locality these

infections are more or less seasonal, and it is only in the malarial season that the use of quinine may be imperative. Thus in temperate regions, and in the subtropics, for periods of from four to five months, the use of the drug as a prophylactic may be omitted with comparative safety.

The development of resistant strains of plasmodia following the use of small doses of quinine, continued for a long period of time, is possible, and for this reason the writer does not believe in using doses of one and two grains daily, as has often been the practice. However, there is no possibility of the development of such strains if initial infections are properly treated.

Quinine prophylaxis is a valuable method of preventing malaria and the drug should be supplied by the State to those who are too poor to buy it, as is done in Italy and Greece. The results of quinine prophylaxis in Italy have proved beyond question the value of this method, and Celli claims that the issue of quinine by Italy has saved no less than 7500 lives and that of 59,340 persons taking daily doses of quinine of 0.4 gm., only 5.8 per cent. developed malaria, including both initial infections and relapses.

4. *Treatment of Initial Infections and of "Carriers."*—A very large proportion of latent malarial infections are the direct result of improperly treated initial infections. While, in many instances, the plasmodia may be found in the blood for several days before the onset of the initial attack, it is a fact that most latent infections have been preceded by one or more acute attacks of fever. The profession is very largely to blame for these cases in civilized regions, for if the initial attack had been properly treated no plasmodia would have survived and the latent infections would have been prevented. The practice of regarding malarial infections as cured because symptoms have disappeared is a most common and pernicious one, and is responsible for the transmission of a very large proportion of malarial disease. Nothing is more common than to see malarial patients walking about and attending to business after only a few days of treatment, inquiry eliciting the fact that the physician has given no directions regarding the necessity of the continued use of quinine or directions for such use. All malarial infections are resistant to treatment; the mere disappearance of symptoms is no index of the entire destruction of the plasmodia present; and a continued course of quinine is necessary to rid the patient of even the mildest infection.

The proper treatment of these latent infections, or of malarial "carriers" as they may be called, is of the greatest prophylactic importance. In cases in which *gametes*, or the forms which undergo development in mosquitoes, have developed, treatment is much more difficult than when they are absent, as these forms are more resistant to quinine. The researches of Darling and of Thompson indicate that large doses of quinine administered daily will reduce the number of *gametes* to a non-infectious minimum, but it takes from 20 to 30 grains of quinine per day, continued over two, three, or four weeks, to do this, and thus, in many instances, treatment to be efficient is almost a cruelty to the patient. However, all latent malarial infections should be treated as acute infections, for these cases continually infect mosquitoes.

5. *Screening of Houses.*—The screening of habitations in regions in which the malarial fevers are endemic is a most valuable prophylactic measure, the objection to it being the expense involved, but the neglect of the measure is in the end more expensive. Copper wire should preferably be used in screening, or, if this cannot be obtained, ordinary iron wire screening covered with two coats of good paint to prevent rusting. The wire screening should contain sixteen meshes to the inch, which is sufficiently fine to prevent the passage of the *Anopheles*, but in regions where the yellow fever mosquito (*Stegomyia fasciata*) is present, eighteen mesh netting should be used, as this species passes through the sixteen mesh.

6. *Education of the Public.*—All of our methods of malarial prophylaxis depend for their success upon the support of the public, and it is the duty of the medical profession to offer every means available to the public for their education in the prophylaxis of these fevers. Such educational measures should originate in the State and local Boards of Health, and should consist in addresses by qualified physicians; the issue of educational bulletins; the enlistment of the press, in the interests of publicity; and the notification of malaria to health authorities, in the same manner as any other infectious disease. Such notification would focus the attention of the public upon the immense harm done to a locality by the presence of malarial infection. The teaching of the essentials of malarial prophylaxis in the public schools is a most important and useful method of prophylaxis. The young are receptive and there is no better way of interesting the parents than by the instruction of the children.

Personal Prophylaxis.—By personal prophylaxis we mean measures which the individual himself may take in order to prevent infection, or, in other words, to prevent being bitten by mosquitoes. If one is obliged to travel in malarial districts, the season of the year in which such fevers are less prevalent should be selected, if possible, and travelling should be done in the daytime. In selecting camp sites and sites for buildings, high, well-drained land should be chosen. If mosquitoes are numerous it is better to sleep above the ground floor. In tropical regions the use of punkas, or fans, as well as, where obtainable, electric fans, is serviceable in keeping away the mosquitoes. For the protection of the hands and face during the day, or when travelling at night, odorous substances may be employed, these being smeared on the skin and renewed when needed. Among the most useful are oil of citronella or pennyroyal, camphor, oil of eucalyptus, oil of anise, and kerosene. Pyrethrum powder should be burned before retiring, in rooms in which mosquitoes are present. Individuals in malarial localities should always sleep under a mosquito net.

One of the most important aids in personal prophylaxis is the use of quinine. The drug should be given in doses of from 5 to 6 grains (0.30–0.35 gm.) every day, or in larger doses, 8 to 10 grains (0.50–0.60 gm.) two or three times a week. In the vast majority of instances the prophylactic use of quinine will prevent malarial infection, but a few individuals, despite its use, succumb to the infection. Some individuals cannot take quinine regularly without suffering disturbance, and in such instances

some substitute may be used, such as thiocol or methylene blue. Neither of these agents, however, is as useful as quinine.

Treatment.—This may be divided into hygienic and medicinal. While the medicinal is altogether the most important, hygienic measures should always be combined. Fortunately, in the malarial infections we have a specific which is generally successful, when properly administered, in curing the disease. Perhaps no drug is as true a specific in any disease as is quinine in malaria. There are rare instances in which it seems to be powerless to limit the course of malarial infection, but a careful examination will prove that if it is administered in the proper manner it is efficient in these cases as in others. Thus, certain individuals cannot absorb quinine through the stomach, but in such persons the hypodermic administration will result in a cure of the infection, and thus it is that the successful treatment of malaria by quinine depends almost entirely upon the proper administration of the drug.

The mild intermittent malarial infections, such as the tertian and quartan, tend toward spontaneous recovery. In many instances of infection by the tertian and quartan plasmodia, recovery may occur without the aid of medicinal measures, but these infections may become pernicious, and even if they do not, the occurrence of repeated paroxysms of the fever results in a diminution of the vitality of the patient, as evidenced by the anemia which invariably accompanies such repeated attacks. Thus it is important that every malarial infection should be treated medicinally and not left for nature to cure.

Hygienic Treatment.—It is undoubtedly true that in all malarial infections, however mild, rest is most important, and the patient should be confined in bed until the active symptoms have disappeared. While this is not essential in some of the mildest tertian and quartan infections, it should always be followed out in cases of estivo-autumnal infection. Treatment by quinine is always much more effective when the patient is confined to bed, recovery is always more rapid and permanent, and the danger of pernicious symptoms is also much lessened. In all cases of malarial infection the sick-room should be, if impossible, in an upper story, well ventilated and thoroughly screened, thus limiting the chances of infection to others.

The diet should be light while there are any active symptoms present, consisting of milk, soups, custards, soft-boiled eggs, etc. A light diet should be persisted in until the temperature has been normal for at least a day, and then a more liberal diet is indicated. The more nutritious the diet is the better, as in many cases the debility and anemia are remarkable.

It is a good plan to secure a complete evacuation of the bowels coincident with or before the administration of quinine. The administration of calomel until the bowels move freely not only serves to better the patient's condition, but also renders the action of quinine much more efficient. It hastens and favors the absorption of the drug.

Medicinal Treatment.—In the vast majority of malarial infections but one drug need be considered, that is quinine, and by quinine any derivative of cinchona bark is meant. In considering the therapeutical

uses, the following points should be discussed: (1) the action of quinine upon the malarial plasmodia; (2) the choice of preparation; (3) the time of administration; (4) the methods of administration; (5) the dosage; and (6) contra-indications.

1. *The Action of Quinine upon the Malarial Plasmodia*.—Quinine exerts its beneficial action upon malarial infections by directly destroying the malarial plasmodia. This may be summarized as follows:

Plasmodium Vivax.—(Tertian Plasmodium).—In the living specimen the administration of quinine in therapeutic doses causes an initial stimulation of amœboid movement in the parasite, followed by a decrease in activity, and finally cessation of motion; granular degeneration of the cytoplasm follows, and eventually the parasite undergoes fragmentation; extrusion of these fragments from the infected erythrocyte follows. In organisms not destroyed, there is less pigment developed and sporulation is atypical, in that a smaller number of *merozoites* are produced. The *gametes* present no changes in morphology after the administration of quinine, but none develop if sufficient of the drug be administered at the beginning of the infection.

In stained specimens the following changes may be noted after the administration of quinine: The cytoplasm stains a more intense blue, the chromatin of the nucleus stains an almost black color, and fragmentation of the parasite is clearly demonstrated. Atypical sporulation, as evidenced by a smaller number of *merozoites* and the absence of chromatin from many of the *merozoites*, is frequently observed. Similar changes are observed in stained specimens of young *gametes*, but the fully developed *gametes* present no morphological changes.

Plasmodium Malariae.—(Quartan Parasite).—The action of quinine is identical with that observed in the tertian plasmodium and the writer has not observed any morphological evidence that this species is more resistant to quinine than the tertian parasite.

Plasmodium Falciparum and *Plasmodium Falciparum Quotidianum*.—(Tertian and Quotidian Estivo-autumnal Parasites).—The effect of quinine upon these two species is identical. In the fresh blood the organisms appear more refractive after quinine has been administered, and at first amœboid activity is greatly stimulated, but later is entirely lost. The cytoplasm appears more granular than normal, and in the pigmented parasites marked evidences of degeneration are observed. In stained specimens the cytoplasm stains intensely blue; while the chromatin stains dark violet instead of the ruby-red color normally observed. Extrusion of the chromatin is sometimes observed, while the vesicular portion of the nucleus is absent. In the pigmented and sporulating parasites the changes are similar to those described for the tertian and quartan parasites, consisting of a granular degeneration of the cytoplasm which stains an intense blue; decrease in the amount and atypical staining of the nuclear chromatin; fragmentation of the plasmodia and decrease in the number of *merozoites* produced in the parasites not killed by the drug. The writer has never observed any morphological changes in the crescents or *gametes* when fully developed, but in the intracellular early stage quinine is capable of killing them. Intra-

corpuscular conjugation appears to be prevented by quinine early in an infection.

In summary, it may be stated that quinine affects the malarial plasmodia at every stage in their development up to the pre-sporulating stage and the fully developed *gamete*. If the drug acts directly upon the *merozoites* the vast majority of them are destroyed, and those that escape are apt to be badly crippled, as shown by atypical development and the decrease in the number of spores in the sporulating stage. The prevalent idea that quinine cannot act upon the plasmodia after they have invaded the erythrocytes is erroneous, and it is my opinion that the drug greatly hinders the development of the parasites while they are intracellular and thus produces the many atypical sporulating forms observed after its administration. It has not been proved, but there is some ground for believing, that the exhibition, for a long period, of doses of quinine insufficient to kill the plasmodia may result in the development of quinine-fast strains and that these strains furnish the explanation for the cases of malaria that are very resistant to the drug and that relapse frequently despite all treatment.

2. *Choice of Preparation*.—Of the many salts of quinine, but three are really deserving of attention, in that they are generally available and of practical use. These are the sulphate, the dihydrochloride, and the tannate. For general use the sulphate is usually preferred, as it is cheap and reliable in its action, but it has the disadvantage of being very insoluble and irritating to the stomach. The dihydrochloride is very soluble (1 part to 0.96 parts of water) and should always be used when the drug is to be administered hypodermically. The tannate is an excellent salt for administration to children, put up with chocolate in the form of troches or a confection. Nardelli claims that this salt is the best for use as a prophylactic as it is absorbed more slowly and is more completely oxidized than any other salt of quinine; this opinion is concurred in by Celli, who states that it is the ideal salt for prophylactic purposes.

3. *Time of Administration*.—The drug acts upon practically every stage of development of the parasites, being most effective upon the *merozoites* and the young intracellular forms. It follows that the best results will be obtained if the drug is present in the blood continually, and this is best secured by the administration of quinine at regular intervals throughout the twenty-four hours. While good results are secured in uncomplicated tertian and quartan infections by one large dose just before the expected time of sporulation, they cannot be compared to the results obtained by the interrupted administration of the drug, and in estivo-autumnal infections the interrupted method is the only one that should ever be adopted. The discomfort to the patient is much less when the drug is given at regular intervals and the remedial results are much more lasting. To secure the best results quinine should be administered in *acute* attacks every three or four hours, in the proper dosage, until the symptoms have disappeared, when it should be administered morning and evening for some days and then as recommended in discussing the dosage of the drug.

4. *Methods of Administration.*—This may be by the mouth, by the rectum, subcutaneously, intramuscularly, and intravenously.

By the Mouth.—This is the method usually employed, and, with the exception of pernicious cases, there are very few instances in which the drug cannot be administered in this way with good results. When given by the mouth, quinine may be administered in the form of a solution, capsules, wafers, pills, troches, and a confection. Pills should never be administered, as they are apt to be insoluble. The same criticism applies to tablets and troches, unless one can be sure that they are freshly made. It is best to give the drug in solution, if possible, the sulphate being used and dissolved by adding a drop of dilute hydrochloric acid to each 0.065 gm. (gr. j) of the drug. If, for any reason, the solution cannot be employed, capsules or wafers are satisfactory, the chief objection being that the drug is liberated *en masse* in the stomach and may prove irritating. However, this may be disregarded from a practical standpoint. In patients who cannot take the sulphate, and in children, the use of troches of the tannate of quinine is indicated.

Rectal Administration.—This method is only mentioned to be condemned, as it is practically useless.

Subcutaneously.—This has been employed quite largely but should be abandoned. It has been repeatedly shown that when the drug is introduced in the usual dose, either in the subcutaneous tissue or intramuscularly, a coagulum results, the greater part of the dose becoming useless, while there is always danger of abscess formation, and indurations are produced that are sometimes permanent. Absorption and oxidation of the drug are less when thus introduced than when taken by the mouth, so there is no good reason for this method save in those very rare instances in which the drug cannot be taken by the mouth, and then in my opinion the intravenous method is preferable. If, however, it is found that this is the only way in which quinine can be administered, it is much better to give the drug intramuscularly than subcutaneously.

Intramuscularly.—Koch first recommended this method and though it possesses the disadvantages mentioned for the subcutaneous method, it has the advantage that abscesses are less apt to follow. There is also some evidence to show that less of the drug has to be given and that the results are better from a remedial standpoint. The salt of quinine to be used in any hypodermic method of administration should be easily soluble and for this purpose the dihydrochloride is the most suitable. The following solution should be used for injection:

R—Quinine dihydrochloride	5 gm. (gr. lxxv)
Normal salt solution	10 gm. (ʒiiss)

In this solution 1 cc. (Mxxv) contains 0.5 gm. (gr. viiss) of the drug. In using the solution the required amount is diluted three or four times with normal saline solution and injected deep into the muscle, the glutei being generally selected.

In giving quinine either intramuscularly or intravenously, the utmost care should be taken that strict asepsis is preserved. The syringe should be a glass one, properly graduated, and sterilized just before

use. The salt solution should be made from freshly distilled water and also sterilized. The skin over the region to be injected should be washed with hot water and painted with tincture of iodine. The quinine should be dissolved in a small amount of absolute alcohol which practically sterilizes it, and should then be placed in the requisite amount of salt solution. The fluid should be injected slowly, and after the needle is withdrawn the site should be touched with tincture of iodine.

Intravenous Injection.—This method was first introduced by Baccelli, and it is the one which has proved most useful whenever it is desired to secure the most prompt effects of the drug, as in the treatment of pernicious infections. This method should be reserved for pernicious infections or for patients who cannot take quinine by the mouth, but further research may prove that it is possible to kill all the plasmodia by one or two intravenous injections of some preparation of the drug, or, perhaps, by some new derivative of quinine, or other drug, and if this can be accomplished the intravenous method of administration will undoubtedly replace the other methods in use at present.

The solution usually recommended is that of Baccelli, containing 1 gm. of dihydrochloride of quinine, and 10 cc. of normal salt solution, the entire amount being injected into a vein. While thousands of cases of malaria have been thus treated with good results, some deaths have occurred, and it has been generally accepted that these deaths were due to the great concentration of the drug. Accordingly it is advised that Baccelli's solution be diluted at least in the proportion of one part of quinine to 500 parts of normal salt solution as follows:

R—Quinine dihydrochloride	1.0 gm. (gr. xv)
Normal saline solution	500.0 gm. (℥ xvi)

The salt solution must be made of freshly distilled water and sterilized after the addition of salt, and it should be lukewarm when injected.

The most careful precautions should be taken to maintain asepsis. The solution should be placed in a glass vessel of suitable capacity, open at the top, connected with a rubber tube in which is a glass window, and to which is attached a stop-cock and a suitable needle. The whole should have been sterilized before the solution is put into the vessel, a small piece of absorbent cotton being placed at the bottom of the container over the entrance of the rubber tubing. The skin over a large vein of the forearm is washed with hot water and painted with tincture of iodine. The vessel containing the quinine solution is elevated and a little of the solution allowed to flow through the tube, thus filling the needle, which is now introduced through the skin over the vein and then passed directly into the vein, being careful to keep the needle as nearly parallel with the forearm as possible. The solution is now allowed to flow into the vein slowly, governing the flow with the pressure of the finger on the tube or by the stop-cock. The entire amount of quinine solution should be injected with the exception of a few cubic centimeters left in the irrigator. The needle is then withdrawn, the site of the puncture painted with tincture of iodine, and a collodion dressing

applied. The quinine is best dissolved in a small amount of absolute alcohol before it is added to the salt solution. This method appears to be devoid of danger and should be preferred to the intramuscular method. As quinine is a heart depressant, it is well to give strychnine hypodermically just before the injection.

5. *The Dosage of Quinine.*—It is probably true that there is no other drug which has been more abused as regards dosage than quinine. Almost invariably the chief fault has consisted in giving too much of it, doses of from 5 to 6 gm. (gr. 75 to 90) not infrequently being given during twenty-four hours. The use of such large amounts is never required and instead of doing good they greatly increase the discomfort of the patient. The writer has never observed a case of malarial fever in which it was necessary to give over 2.5 gm. (gr. xl) of quinine in twenty-four hours, and 2 gm. (gr. xxx) of the drug, properly administered during the twenty-four hours, and continued for three or four days, is sufficient for any ordinary case of estivo-autumnal malaria, while 1 gm. (gr. xv), given just before the paroxysm, and continued in divided doses through the twenty-four hours for the next few days, will be sufficient for most cases of tertian and quartan infection, so far as the symptoms are concerned.

General Scheme of Treatment.—In *tertian* and *quartan* malaria the best results are secured by giving quinine in doses of 0.32 gm. (gr. v) every four hours until from 1 to 2 gm. (gr. xv to xxx) are given within the twenty-four hours, and this dosage continued until all symptoms disappear. Thereafter the drug should be continued for at least three months, the dose being gradually diminished during the first two weeks after the symptoms have disappeared until the patient is taking 0.32 gm. (gr. v) per day at the end of the second week, and this dose should be continued for two weeks longer. Thereafter 0.5 gm. (gr. viiss) of quinine should be taken every seventh day, on retiring, until three months have elapsed from the cessation of acute symptoms.

In *estivo-autumnal* infections in which the symptoms are not pernicious in character, quinine should be administered by the mouth in the form of a solution or capsules. If 0.32 gm. (gr. v) is given every three or four hours until the active symptoms have disappeared, and repeated every five or six hours for three or four days thereafter, rapid recovery results in most cases. However, although symptoms have disappeared, the infection is still present, and the quinine must be continued. During the next week the drug should be given in doses of 1 gm. (gr. xv) every other night on retiring, and for at least three months thereafter the same dose should be administered upon the evening of every seventh day.

If quinine is given in the manner described we may expect a cure in most of our cases of uncomplicated malaria, but unless some such rigorous method of keeping up treatment is adopted, relapses will almost invariably occur and eventually the patient will become a *gamete* carrier, and thus a transmitter of the infection.

The treatment of *latent* and *recurrent* cases is exactly that of acute cases so long as the plasmodia are present in the blood, and then a course of quinine should be given for two or three months, as already described.

The treatment of "*gamete carriers*" is still an open question. Both Darling and Thompson agree in stating that large doses of quinine will reduce the *gametes* in the peripheral blood to a non-infectious minimum, and eventually cause their disappearance. The amount of quinine required to accomplish this is large, 2 gm. (gr. xxx) every day for three or four weeks being the quantity recommended by Thompson. In view of the results obtained by these observers all *gamete carriers* should be thus treated, if it be possible.

When the intravenous method of treatment is resorted to the dose should be from 0.5 to 1 gm. (gr. viiss to xv), and if no improvement occurs in the symptoms in the course of five or six hours, the dose should be repeated. As a general rule, if the drug is going to prove effective a marked improvement is noted in the condition within that time.

In children the dose should be proportioned to age. Under one year of age the usual dose is 0.032 gm. to 0.065 gm. (gr. ss to j), repeated as in an adult. In older children the drug is well borne, and in pernicious infections proportionately larger doses may be given with good results.

Contra-indications to the Use of Quinine.—In rare instances the administration of quinine is contra-indicated because of some idiosyncrasy to the drug. In some people this drug acts as a violent poison and in them some substitute must be employed. If the use of quinine is followed by amaurosis, deafness, dyspnœa, syncope, hematuria, or hemoglobinuria, it should be discontinued, or if there is a clear history of such complications it should not be given. Pregnancy is not a contra-indication to the administration of quinine, although often stated to be so. The fear that the drug will cause abortion is not well-founded, for if carefully given the risk is not as great in this direction as if the malarial infection is allowed to continue. In malaria presenting pernicious symptoms in pregnant women, quinine should be given intravenously, for the mother's life is endangered, and under such circumstances it is justifiable to disregard that of the child.

Substitutes for Quinine.—Although numerous substitutes have been announced, not one of them is as efficient as the drug itself. *Phenocoll* is sometimes useful in tertian and quartan infections, but should not be used in estivo-autumnal malaria. The dose is from 1 to 3 gm. (gr. xv to xlv), distributed over the twenty-four hours. It is a heart depressant, and for this reason its administration should be carefully watched. *Methylene blue (medicinal)* is a useful drug in the milder infections, but in severe estivo-autumnal malaria it is of little value. Its use is not unattended with danger, as in improper dosage it may produce strangury, albuminuria, and severe diarrhœa. The dose, given in capsule with a little powdered nutmeg, varies from 0.15 to 0.2 gm. (gr. iiss to iij), repeated every four hours. The patient should be warned that after taking the drug the urine will be colored blue. Some proprietary salts of quinine, as *euchinin*, *salochinin*, and *aristochin*, are useful substitutes, but are not as efficient, and are expensive. Their use is not without danger, and symptoms are produced much like those from quinine.

Salvarsan and *neosalvarsan* have recently been urged as specifics for malaria. The most recent and reliable investigations appear to prove

that in tertian malaria these drugs are efficient, but that they are useless in quartan and estivo-autumnal infections. *Atoxyl* has been experimented with in malaria, and found not only useless but dangerous.

Treatment of Special Symptoms.—During the *cold* stage of the attack, the external application of heat in some form is grateful, while in the *warm* stage great relief is afforded by sponging the patient with tepid or cold water. High temperature should always be controlled by the cold bath, and the physician who uses antipyretics for this purpose submits his patient to an unnecessary danger. If nervousness is marked or the headache is very severe a hypodermic dose of morphia may be given. Symptoms of collapse, which usually appear during the decline in the fever, should be combated by the external application of heat, strong coffee, the hypodermic use of normal salt solution, brandy, and strychnine. Atropine is a valuable stimulant in these cases and should be preferred to strychnine. In pernicious infections, after quinine has been administered intravenously, the patient should be treated symptomatically. Collapse should be treated as indicated; in the *choleraic* form, opium should be administered to check the diarrhoea, and normal salt solution should be injected intravenously or subcutaneously, in addition to the ordinary use of stimulants. Severe vomiting may be treated by mustard plasters applied over the epigastrium, the sucking of cracked ice, and the hypodermic injection of small doses of morphia.

Treatment of Malarial Cachexia.—The occurrence of malarial cachexia in a person who has been treated for the acute attacks of malaria preceding the development of cachexia is a reproach to the physician, for had proper treatment been given at that time the conditions following numerous relapses could not have occurred. The best treatment of malarial cachexia is removal to a non-malarial locality, preferable to a high, dry region, with a bracing climate. The administration of tonics and proper hygiene regarding clothing, exercise, and food are of great importance. Quinine should be administered as long as the patient is exposed to reinfection or the plasmodia can be demonstrated in the blood. The food should be of the most nutritious character and the patient should be urged to eat if the appetite is poor. The administration of Warburg's tincture is often of service, not so much because of the small amount of quinine it contains but because of its tonic properties.

In conclusion, the fact is emphasized that no substitute for quinine can equal it in treatment of malaria, and that in the worst cases the proper administration of this drug will result in prompt recovery, provided the patient be seen in time. There are one or two substitutes for the drug which may be used in very rare instances where quinine is contra-indicated, but the writer believes with Osler, that, "the physician who at this day cannot treat malarial fever successfully with quinine, should abandon the practice of medicine."

CHAPTER III

BLACKWATER FEVER

BY J. W. W. STEPHENS, M.D. (CANTAB.)

Introduction.—In our opinion, blackwater fever, wherever seen, is one and the same condition, and the symptoms vary from trifling or insignificant to most grave and fatal. We do not believe that mild cases are due to one cause (quinine hemoglobinuria in malarials) and severe cases to some other cause or causes. The main symptoms are: (1) hemoglobinuria, (2) bilious vomiting, (3) jaundice, and (4) fever.

Geographical Distribution.—This is still incompletely known. No data, as a rule, exist to enable one to determine its frequency in relationship to susceptible population, malarial or other morbidity. In general terms its occurrence coincides with that of the severe forms of malarial infection.

Etiology.—Although our knowledge of the actual condition which leads to the attack is quite obscure, yet on the other hand we believe the evidence is equally clear that this condition only occurs in those who have previously suffered from malaria, and it is clear also that quinine frequently brings on the attack, but how we do not know. The evidence for the malarial factor in this disease is the following:

1. The distribution of this disease and of severe malaria is identical, and this becomes more and more clear as our knowledge of the distribution of the disease becomes more extensive. One of the best tests of the existence of severe malaria in a country is the endemic index (parasite rate) of native children, as used originally by Stephens and Christophers. One example must suffice; the endemic index on many tea-gardens in the Duars, Bengal, approaches 100 per cent., and the conditions of life are such that *continuous* infection of Europeans with malaria is the normal state of things. Blackwater fever is there a common disease. The endemic index of the Tonkin Delta Provinces as a whole is 3.17 per cent. (in certain regions rising to 19 per cent.), and blackwater fever is exceptional there, but in the Upper Tonkin provinces as a whole the endemic index is 31.86 per cent., in some districts rising to 43 per cent., and there blackwater fever is frequent.

2. Blackwater fever is, moreover, usually but perhaps not always associated with a high rate of prevalence of the malignant tertian parasite. In Upper Tonkin (Sonta province) the malignant tertian rate is 71 per cent., while in the Tonkin Delta the malignant tertian rate is 10 per cent.; simple tertian, 90 per cent.

3. The association of malaria and blackwater fever is also shown by their frequency in Americans and Europeans respectively in the Panama Canal Zone. Although exact figures are not available for malaria, yet

the statement is undoubtedly true that the unprotected Europeans suffer far more from malaria than the protected Americans. As regards blackwater fever the average rate was four times as great in Europeans as in Americans from 1905 to 1909, in 1909 more than twenty times as great, and from 1910 to 1913 thirteen times as great.

4. Blackwater fever, while occurring in the first year of residence or even in the first six months, in the majority of cases is a disease of the second or third year, as the following figures show, though open to some criticism, as no correction has been made for the population in the various years, owing to the incompleteness of the records in many instances.

Out of 1126 cases, 76 occurred in the first six months, 224 in the first year, 346 in the second year, 259 in the third year, 106 in the fourth year, 40 in the fifth year, 75 in the sixth year and later, giving the following percentage:

	Per cent.
First six months	6.7
First year	19.8
Second year	30.7
Third year	23.0
Fourth year	9.5
Fifth year	3.5
Sixth year	6.6

5. Blackwater fever is not to be regarded as an especially severe attack of malaria, though hemoglobinuria may occur during such an attack, but it occurs, as a rule, in those more or less constantly suffering from slight attacks not properly treated by quinine. Considering how often quinine has been taken previous to the attack, and how often in repeated doses, it would not be astonishing if parasites were seldom found, especially as it is generally agreed that even if present they rapidly disappear. The actual findings in regard to parasites as deduced from all the cases in which definite statements are made are the following:

Day before hemoglobinuria.		Day of hemoglobinuria.		Day after hemoglobinuria.	
Cases.	Positive.	Cases.	Positive.	Cases.	Positive.
67	49	162	77	160	37
73 per cent.		47.5 per cent.		23 per cent.	

The following data of Deeks and James in regard to malaria parasites are also very instructive:

	Cases.	Positive.	Percentage.
Amoebic dysentery	260	48	18.4
Liver abscess	79	7	10.0
Typhoid fever	33	4	12.0
Blackwater after admission onset	102	60	59.8
Blackwater present on admission	113	27	23.8
Malaria	40,928	23,410	58.0

6. Seeing that parasites rapidly disappear in blackwater fever, Stephens and Christophers applied two other tests for the detection of malaria, viz., the presence of pigmented leukocytes and an increase in the percentage of large mononuclear leukocytes. It has been hastily said by certain authors that the latter sign is simply a sign of a protozoal infec-

tion; while the evidence is wanting that this is true as a general statement, yet as in some cases it may be true, we will confine ourselves to pigment only as evidence in the absence of parasites. Christophers and Bentley give the following example. Although the figures are small, yet Stephens and Christophers have published similar results.

	First day.		Second day.		Fourth to sixth day.	
	Cases.	Positive.	Cases.	Positive.	Cases.	Positive.
Parasites only	10	6	7	0	10	1
Pigment	10	8	7	6	10	4

7. Postmortem evidence: In 31 cases with definite statements as to the presence or absence of malaria pigment, pigment was found in 26, *i. e.*, in 83.8 per cent. It may be argued that the remaining 16.2 per cent. were non-malarial, but in the presence of the other evidence we must hesitate to accept this conclusion, and wait for further observations.

8. The importance of determining the essential factor in the production of blackwater fever is not merely of scientific but of the greatest practical importance, for if, as we believe, it is malarial in origin, then it can be avoided. Besides general statements which may be, however, quite true, *e. g.*, blackwater fever has disappeared from certain parts of Algeria with the decrease in malaria following anti-malaria measures,¹ we may quote the following facts in support of this position. The following, compiled from Plehn's data in the Cameroons, shows the effect of quinine prophylaxis.

	Attacks of malaria.	Interval between attacks in months.	Blackwater attacks.	Interval between attacks in months.	Deaths from blackwater fever.
Unprotected	287	2	31	18.5	10% about
Protected	90	5	6	74.0	0

These arguments might be added to and enlarged upon, but in our opinion their cumulative force proves the *malarial origin* of blackwater fever. This has been vigorously denied by those who hold to the special parasite hypothesis, but is now admitted by some of these. The question, as we have said, is not merely a scientific one, but has a great practical bearing, and we consider that much mischief is done by promulgating such an hypothesis on no ascertained data.

Three instances have been given by authors as examples of countries where malaria exists, but no blackwater fever, *viz.*, Egypt, Ceylon, and the Philippines. It is true that there is no blackwater fever in Egypt, but neither does malaria occur there, or, at any rate, to any appreciable extent, *e. g.*, during three months' work at the large Kasr-el-Ainy Hospital in Cairo, I saw only 2 cases of malaria, and both these had come from the Sudan. In regard to Ceylon and the Philippines, blackwater fever *does* exist in both these countries; so far as our present data go, it is rare in both places, but we require further information. No instance has been adduced of the existence of blackwater fever in a country

¹ Ed. Sergent, private communication.

without malaria. Finally, it is quite possible that the endemic index of a country might be very high and yet the mode of living of susceptible Europeans such that they would not contract malaria.

The Quinine Factor.—Here again plain facts have been met with obstinate denial by many authorities. It is now, however, admitted that quinine *can* produce hemoglobinuria. We believe, however, that until the underlying pathological condition is understood it can hardly be proved that this is the commonest cause; it also appears that in a certain number of cases quinine can be excluded as a factor. As to the mode of action of quinine Barrat and Yorke calculate that it does not act directly in the circulation as the amount required to do this would be 3 grams per kilo of body weight, a fatal dose.

Frequently there is a history of exposure to the sun, unwonted exercise, fatigue, chill, alcoholism, change of locality, etc.

Pathology.—The spleen is enlarged, with an average weight of 400 grams, and may exceed 1000 grams. The Malpighian bodies may be very prominent and necrosed to a greater or lesser degree. The necrosis is evidenced by presence of fibrin, nuclear remains, leukocyte invasion, and œdema. Necrosis of the pulp may also occur. Melanin is scanty or abundant, occurring in phagocytes. Hemosiderin may also occur. Immense phagocytes crowded with nuclear remains, cell debris, red cells and leukocytes occur in the necrosed areas. Pigmented leukocytes and parasites may be found postmortem when absent from the blood during life. Pigment is usually abundant, but in some cases it can only be found after long search, if at all.

The *kidneys* are usually a little enlarged and on section the medulla may show distinct brownish radiating lines, due to deposits in the tubuli recti, and the cortex brown dots. The microscopic changes are not constant but the following may be seen: The *glomeruli* show (a) distension, and (b) varying amounts of albuminous exudates, granules, or "altered hemoglobin" globules between the tuft and the capsule. The *tubuli contorti* show (a) dilatation and flattening of the epithelium, (b) the epithelium granular and slightly swollen, or (c) distinctly necrotic, the nuclei of the regenerating epithelium showing mitotic figures; (d) with this œdema of the connective tissue and invasion of migratory cells (nephritis), (e) the *lumen* of the tubules practically always contains a finely granular coagulum of albuminous material or brownish globules of "altered hemoglobin" up to 5μ in diameter, with desquamated cells scanty or numerous. This granular material is probably secreted by the epithelium of the tubules. By some authors these granules have been found to give the iron reaction, by others not, the difference possibly depending upon the length of time that has elapsed since their formation; Stieda records granules giving an iron reaction in the epithelium itself.

The *tubuli recti* show (a) plugs or casts of dark reddish-brown, granular material (altered hemoglobin) 40 to 80μ in diameter; sometimes these plugs appear to be hollow. The granules of which they consist are not larger than those in the convoluted tubes. (b) The epithelium is generally unaltered, but there may be a variable amount of desquamated cells in the lumen and separation of epithelium from the basement membrane

The *liver* is usually somewhat enlarged, and averages 2000 grams in weight. The liver cells may show a little fatty degeneration, and they generally contain more or less golden yellow pigment (hemosiderin). Focal necroses of considerable extent are not uncommon. The capillaries are often dilated with blood, and may contain masses of leukocytes, and thrombosis of the sublobular veins occurs. Melanin occurs in phagocytes, which also contain red cells and cellular debris, and in Kupfer's stellate cells. The bile capillaries are generally distended with plugs of yellowish or greenish material.

The *bone-marrow* has a color uniformly red or purplish or mottled when the fat cells have not been entirely replaced by the marrow cells. It is, in fact, nearly always hyperplastic (mainly, however, erythroblastic). Large phagocytes containing melanin, nuclear fragments, and red-blood cells are found. A practically constant and striking change is the great relative increase in eosinophile cells (mononuclear and polynuclear, and the abundance of normoblasts and megaloblasts—Whipple). Melanin is always (?) found, though sometimes careful search is necessary.

The *brain* is usually pale, but shows no parasites or pigment unless the blackwater fever has been immediately preceded by acute malaria with parasites in the blood, when much pigment and many parasites are found in the capillaries.

Symptoms.—Prodromal Illness.—This is nearly always present and cannot be distinguished from an ordinary attack of malarial fever. It usually lasts some days, and the patient has nearly always already treated himself with much quinine before being seen.

Fever.—The attack begins with one or more shivering fits, persisting, it may be for some hours, the temperature rising rapidly to about 103° to 105° F., or even higher. In some cases the rise is only a degree or so and in other cases the course may be afebrile. The temperature curve is usually an atypical, irregular one, intermittent or remittent, but in other cases the curve is distinctly quotidian or tertian. In a day or so, or even in a few hours, as the urine clears the temperature falls, and there is more or less profuse sweating and intense weakness. The attack is usually accompanied by great restlessness, mental anxiety, shortness of breath, and pains in various regions, *e. g.*, the loins and epigastrium. Rigors may occur repeatedly during the course of the fever and hyperpyrexia may ensue with fatal results.

Posthemoglobinuric Fever.—Occasionally after cessation of all the usual symptoms, *i. e.*, during convalescence, fever with evening rises of 101° to 102° may ensue and last for some weeks, even ending in hyperpyrexia. What this fever is due to is unknown, possibly in some cases to a secondary infection.

Hemoglobinuria.—Occasionally this is the first indication the patient has that he is really unwell. There may be practically no other sign. These apyretic cases, "quinine hemoglobinuria," are considered by some as distinct from blackwater fever proper, but in our opinion no line can be drawn between these cases and the severe ones with intense initial rigor and subsequent grave symptoms. Usually after a shivering

fit there is an urgent desire to pass water, and the patient then becomes aware that his urine is "red." The amount of urine is usually increased, and micturition is more frequent. The hemoglobinuria lasts from five to six hours, or even the same number of days, or may be confined solely to the first urine passed. The hemoglobin may either gradually disappear, or when decreasing may increase again or after clearing may return with a fresh access of fever either from a dose of quinine or from unknown causes. As many as half a dozen recurrences may follow, and in certain cases they can be produced at will by quinine. In grave cases oliguria develops, gradually passing into anuria or the condition may supervene suddenly. Suppression may ensue even if the urine passed is normal.

Hemoglobin may also occur in the feces, but few data are available as to this. Urobilin also, besides being excreted in the urine, is, as Simpson has shown, present in large amount in the feces.

Vomiting.—Frequent retching, attended in nearly all severe cases by bilious vomiting, is a distressing symptom, the vomitus consisting of dark green bile. It is accompanied by pain in the epigastrium, and if prolonged produces great exhaustion, and especially if persistent hiccough occurs the prognosis is bad. Thirst and restlessness are often pronounced and tympanites is common and distressing.

Icterus.—Christophers and the writer were never able to detect bile pigment in the urine, and this is the experience of most authors. The yellow color of the blood serum often seen is then not due to bile pigments, but to some other product of hemoglobin. "Icterus" sets in within twenty-four hours after the attack, and is more or less intense, the conjunctivæ and the skin over the whole body becoming a lemon yellow color. In grave cases it is persistent, in slight cases but transient.

Constipation is usually present. The spleen and liver are enlarged. In mild cases the fever, headache, vomiting, and other symptoms gradually subside as the urine clears. In grave cases the fever recurs or persists, the jaundice deepens, thirst is intolerable, and the vomiting is incessant. Hiccough, oliguria leading to anuria, attacks of profuse diarrhœa (reddish), dyspnoea great restlessness, delirium or convulsions, somnolence, and prostration, are conditions which may dominate the scene in particular cases. Death may result from (1) anuria, (2) heart failure, or (3) hyperpyrexia. The mortality can be estimated roughly as about 20 per cent.

Relapses are not uncommon. Half a dozen or so may occur at intervals. *Second attacks* occur in about 10 per cent. of cases. About 60 per cent. occur within the year and 30 per cent. within six months. More than two attacks also occur.

Urine.—The quantity is, as a rule, increased at first and micturition is more frequent. The reaction may be neutral, acid, or alkaline; the specific gravity varies. In color it may vary from a very dark red-brown or almost black porter-color to a brownish yellow. Characteristic is the suspended matter which it contains. This suspended matter (altered hemoglobin) consists of a granular matter of variable color, chocolate, brownish black, light yellow, whitish, and of variable amount. Besides the granular matter, granular casts, 15 to 200 μ long, 3 to 25 μ broad (of the same material), embedded in a hyaline matrix, epithelial casts,

masses, and free epithelial cells occur in varying amounts and not uncommonly a few red blood cells and rarely pus cells and bacilli. The urine usually gives the bands of oxyhemoglobin and sometimes of methemoglobin also. Urobilin is commonly present. It is best detected in the form of zinc-urobilin. Albuminuria may precede and follow the attack, but usually is coincident with the hemoglobinuria. According to Deeks and James, nucleo-albumin, serum albumin, and serum globulin are present in the urine. A peculiarity of the urine is the length of time it resists putrefactive changes. The percentage of hemoglobin in the urine varies from 0.2 to 3.8 per cent., and the total amount of hemoglobin lost from 1.5 to 75 grams (Barratt and Yorke). The amount of hemoglobin in the blood plasma varied from 0.13 to 0.95 per cent., and in experimental hemoglobinuria in the rabbit the percentage in the urine usually surpasses that in the blood plasma, but where the laking of red cells takes place is unknown.

The size of the granules varies from 0.5 to 5μ in diameter and they are brownish in color. In cases of suppression the granular casts are larger, 100 to 150μ by 40 to 60μ , and the granules are coarser and of a dark, reddish-brown color.

Blood.—The red cells may fall below 1,000,000 and the hemoglobin to about 20 per cent. The blood has lost its viscosity so that a good film is often difficult to make. The corpuscles, as a rule, appear quite normal or may present some degree of anemia, their central depression being enlarged. Normoblasts occur and basophilia and polychromasia are frequently seen. In other cases deformed red cells are described, but we have not seen them. In the attack a marked *leukocytosis* (polynuclears, 90 per cent.) may be found, but later a condition of leukopenia exists, and at this time the large mononuclears are increased to 20 per cent. or more. Leishman has described peculiar inclusions, in mononuclear cells (? epithelioid), but they occur in other conditions.

Treatment.—This should be directed from the outset to maintain the secretion of urine, the amount of which should be carefully measured. If the vomiting allows, as much bland drink as possible should be given by the mouth. If this is not possible, warm saline rectal injections (250 cc.) should be given slowly three or four times a day. If this is impossible, owing to diarrhoea or irritation, subcutaneous injections should be used. Warm baths given with great care and tepid sponging are soothing and promote diuresis. Hypodermics of digitalis should be used to maintain the heart's action.

Vomiting is difficult to control. Iced champagne, sucking bits of ice, sinapisms, chloroform water, an ice-bag or hot-water bag to the epigastrium, and morphia, may all be tried. *Constipation* is best treated by castor oil, but one must avoid depleting the system of water.

Quinine is best avoided unless parasites are present in such numbers that the symptoms can in part be attributed to them. During convalescence quinine should be given at first in small doses ($\frac{1}{2}$ to 1 grain daily), gradually increasing the amount. Subsequent to an attack of blackwater fever, chronic malarial patients frequently remain free from malaria for long periods.

CHAPTER IV

TRYPANOSOMIASIS

By COL. SIR DAVID BRUCE, C.B., F.R.S., D.Sc., F.R.C.P.

REVISED BY

GEORGE C. LOW, M.A., M.D., C.M.

Introduction.—Diseases caused by trypanosomes are found over a large area of the earth's surface, from South America, through Africa, Southern Europe, Persia to India, Burma, China, and the Philippines, and affect many kinds of animals, including man. These diseases are caused by the presence in the blood and body fluids of species of flagellated protozoa belonging to the genus *Trypanosoma*. A trypanosome consists of a single cell, and is a sinuous, worm-like creature, provided with a macronucleus and a micronucleus or blepharoplast, a long terminal flagellum, and a narrow fin-like membrane, continuous with the flagellum and running the whole length of the body. The end from which the flagellum protrudes is usually called the anterior; the other end, near which, as a rule, is situated the micronucleus, the posterior. When alive the parasite is extremely rapid in its movements, constantly dashing about and lashing the red blood corpuscles into motion with its flagellum; it moves equally well with either extremity in front. These trypanosomes give rise to an extreme variety of diseases, sometimes so acute as to cause death in a few days, at other times so chronic as to take several years to kill. Some of the species appear to live in the blood of their hosts without causing any perceptible disease, and especially in those species which live in fish, frogs, and other cold-blooded animals. How the trypanosome damages its host is not very clearly known, but the probability is that it gives rise to the presence of small quantities of toxins and so causes, in some animals, chronic inflammatory processes, or in others extensive and rapid destruction of the blood corpuscles. However the damage is done, trypanosomiasis is extremely fatal in man and the domestic animals, such as the horse, dog, and ox. Large native populations in Central Africa are being swept away by this plague, and great tracts of country rendered uninhabitable for man and the domestic animals.

TRYPANOSOMA LEWISI

The Rat Trypanosome.—The earlier discoveries of trypanosomes in the blood of fish and frogs, dating from the year 1841, may be passed over. For about forty years little or no progress was made until Surgeon-

Major T. R. Lewis,¹ F.R.S., Royal Army Medical Corps, made an important observation by finding flagellated organisms in the blood of rats. It was ascertained that each organism consisted of a body portion, and of an extension of it in the form of a gradually tapering, long flagellum. They were found in two species of rats—*Mus. decumanus* and *Mus. rufescens*—and in 29 per cent. of the animals examined. This rat trypanosome is distributed, broadly speaking, all over the world; and even in Uganda, in Central Africa, numbers of the common field rat harbor it. The rat trypanosome does not appear to give rise to any symptoms of disease.

TRYPANOSOMA EVANSI

Surra.—This trypanosome was discovered in 1880 by Evans.² Surra is mainly an Indian disease, occurring in the Punjab and in Burma. It usually appears during the rainy season, and disappears gradually with the advent of the cold, dry weather. The horse and mule are most susceptible, the dog coming next, and these three always succumb to the disease. The camel is supposed to live for three years after becoming infected, while the ox generally recovers after some five or six months. Rogers³ states that surra is carried from sick to healthy animals by species of tabanus, and other writers have stated that stomoxys also acts as an infecting agent. Surra is very closely related to the next disease—nagana—and, in fact, is considered by many to be identical.

TRYPANOSOMA BRUCEI⁴

Nagana or Tsetse-fly Disease.—As the writer of this article had the good fortune to discover this species of trypanosome in 1894, perhaps a few words of personal experience will not come amiss. In October, 1894, when serving in Natal, South Africa, he was asked to go to Zululand to report on a disease which was causing severe loss among the native cattle. The native name of the disease was nagana. At this time no suspicion was entertained that nagana and the tsetse-fly disease were identical. The writer at once proceeded to Zululand and on arrival in the infected area started to examine the affected cattle by the ordinary bacteriological methods. The animals were emaciated, with staring hair, some fever, and sometimes œdema of the subcutaneous tissues of the neck. Examination of the blood and organs for bacteria by microscopic and cultural methods produced no result. Careful daily examinations of the blood were made and it was noted that a peculiar

¹ *Quart. Jour. Micr. Sci.*, 1879, xix, 109.

² *Report on Surra*, published by the Punjab Government, 1880.

³ *Proc. Roy. Soc.*, March 14, 1901, vol. lxxviii.

⁴ Bradford and Plimmer, "The *Trypanosoma Brucei*, the Organism found in Nagana or Tsetse-fly Disease," *Quarterly Journal of Microscopical Science*, 1902, vol. xlv.

stained body, resembling an artistic dolphin, occurred from time to time among the red blood corpuscles. It was thought at first that this object was an accidental appearance due to the stain, but thinking that if the body was a parasite, it might show motion, several specimens of fresh blood were examined. A long search was rewarded by finding a very active body, wriggling and twisting about with great energy among the red-blood corpuscles. It was the first time the writer had seen a trypanosome, and, as then there was little or no literature on these parasites, it was difficult to know how to place it. A comparison with the description and drawing of the rat trypanosome in Lewis' book¹ showed that it was a trypanosome. But there was no proof that the parasite was the cause of nagana; it occurred only in small numbers in the blood of the cattle, and the rat trypanosome lives as a harmless guest in healthy animals. Therefore, the blood of the infected cattle was inoculated into horses and dogs.² The disease in the horse and dog is much more acute than in the ox. In a few days the blood, especially of the dog, was found to be teeming with thousands of trypanosomes. It, therefore, began to appear probable that this parasite might be the cause of nagana. At that time there was no suspicion that this disease among the native cattle, occurring in kraals situated many miles from the "Fly country," was the same disease as that known to travellers as the tsetse-fly disease. The work at this time was being done on the summit of a mountain called Ubombo some 2000 feet above the surrounding low country. The low country to the east of the mountain was known to be infected with the tsetse-fly, and having often read about this disease, it was determined to take a few animals into this "Fly country" and see what the disease was like. Two young oxen, a horse, and several dogs were taken into the heart of the "Fly country." After being there a fortnight the animals were brought back to the top of the mountain and examined in the usual way: their temperature taken, their blood examined, and any symptoms that might occur noted. It was found that the blood of these animals affected with the tsetse-fly disease contained the same parasite as that found in nagana. In this way, after many observations, it was forced upon me that the two diseases, nagana and tsetse-fly, were one and the same.

Experiments were then made to find how the animals became infected, whether the fly was the carrier or a mere concomitant of the unhealthy district, and, if a carrier, if it was the only carrier of the disease from sick to healthy animals. Horses taken down into the "Fly country" and not allowed to feed or drink there took the disease. Bundles of grass and supplies of water brought from the most deadly parts of the "Fly country" to the top of Ubombo and there used as fodder for healthy horses failed to convey the disease. Tsetse-flies caught in the low country and kept in cages on the top of the mountain when fed on infected animals were capable of giving rise to the disease in healthy animals.

¹ Lewis, T. B., *Physiological and Pathological Researches*, 1888.

² Bruce, D., *Preliminary Report on the Tsetse-fly Disease or Nagana in Zululand*, Durban, Natal, 1895, *Further Report*, printed for the Royal Society by Harrison & Sons, London, 1896; *Appendix to Further Report*, Harrison & Sons, 1903.

The question then arose as to where the tsetse-flies obtained the trypanosomes. The flies lived among the wild animals, such as buffaloes, koodoos, and other species of antelopes, and, naturally, fed on them. It seemed that, in all probability, the reservoir of the disease was to be found in the wild animals. Therefore all the different species of wild animals obtainable were investigated by the injection of their blood into healthy susceptible animals, and by examination of the blood itself. It was discovered that many of the wild animals harbored this trypanosome in their blood. The parasites were never numerous, and the wild animals did not seem to be affected by them in any way; they showed no signs or symptoms of the disease, and it therefore appeared probable that the trypanosomes lived in their blood as harmless guests, just as the trypanosome of the rat lives in the blood of that animal.

Nagana affects a large variety of species of animals. With the exception of the baboon, it is fatal to monkeys, horses, mules, donkeys, cattle, dogs, cats, rabbits, guinea-pigs, rats, mice, and other animals.

TRYPANOSOMA GAMBIENSE AND TRYPANOSOMA RHODESIENSE. HUMAN TRYPANOSOMIASIS. SLEEPING SICKNESS

Historical.—The *Trypanosoma gambiense* was first described by the late Dr. J. E. Dutton, in 1901, in a patient of Forde's¹ on the Gambia. The latter observer noted the parasites and showed them to Dutton² who recognized them as trypanosomes and named them the *Trypanosoma gambiense*.

This discovery of trypanosomes in the blood of man awakened a great deal of interest, and Dutton and Todd were sent out to Senegambia to make further investigations. They arrived at Bathurst on the second of September, 1902, and remained on the West Coast for nearly a year. They examined 1043 natives in the Gambia, and found the parasite in 6 cases only. They sum up their report by saying that, taking all the facts into consideration, they believe the disease, as it occurs in natives, to be a peculiarly mild one, and that it is at present impossible to recognize it clinically, and they suggest the possibility that the natives in this disease may bear the same relation to Europeans as does the wild game of Central Africa to domestic animals in the tsetse-fly disease.³

In the beginning of 1903, Baker⁴ noted the presence of trypanosomes in three cases in the blood of man in Entebbe, Uganda. Shortly before this Castellani,⁵ a member of the Commission sent out to Uganda by the Royal Society, London, for the purpose of investigating sleeping sickness, had observed these hematozoa in the cerebrospinal fluid of 5 cases of sleeping sickness, and in 1 of these he had also seen them in the blood. This was the first time trypanosomes had been seen in the

¹ *Journal of Tropical Medicine*, September 1, 1902.

² *Thompson-Yates Laboratory Reports*, 1902, iv, 11.

³ Dutton and Todd, *First Report of the Expedition to Senegambia*, Liverpool School of Tropical Medicine, 1902, Memoir XI.

⁴ *British Medical Journal*, 1903, i, 1245.

⁵ "Presence of *Trypanosoma* in Sleeping Sickness," *Royal Society, Reports of the Sleeping Sickness Commission*, 1903. Harrison & Sons, London.

blood of recognized cases of sleeping sickness. When the writer arrived in Uganda, on March 16, 1903, for the purpose of continuing the investigation of this disease, Castellani described his findings, and consented to stay a week or two longer, in order that this particular point might be pursued. He remained in Entebbe for three weeks, and during this time 22 cases of sleeping sickness were examined, trypanosomes being found in 15, or about 70 per cent.

From this time the history of the *Trypanosoma gambiense* became merged in that of sleeping sickness and it was soon proved that trypanosoma fever was but the first stage of sleeping sickness. Quite recently Stephens and Fantham have described, under the name of *Trypanosoma rhodesiense*, the trypanosome which is found in cases of human trypanosomiasis in Nyasaland and Rhodesia.¹

Human Trypanosomiasis or Sleeping Sickness.—The history of the disease itself may be given in a few words. Human trypanosomiasis or sleeping sickness, known for more than a hundred years on the West Coast of Africa, attracted a good deal of interest and curiosity on account of the peculiar symptoms of lethargy which developed and which gave rise to the name of sleeping sickness. The disease was found to lose its power of spreading from man to man upon removal to a non-endemic area. Different theories were held as to its causation, but all these fell to the ground when it was discovered that the trypanosome was the real cause.

Etiology.—*Geographical Distribution.*—The disease was first reported by Atkins in 1734 on the West Coast of Africa. Since then other observers drew attention to it from time to time, and it was found that it had a much wider geographical distribution than was at first supposed. On the West Coast of Africa it extends from Senegal in the North to San Paolo de Loanda in the South, and in addition spreads into the hinterlands of the different colonies. Large areas of the Belgian Congo are affected and the disease spreads from here across the continent to Uganda. Within the last few years a form of the disease has appeared, or at least has been recognized, in Nyasaland and Rhodesia. It varies in intensity in these different parts and seems to have largely died out on the West Coast or at least become feebly endemic. On the other hand, in Uganda and parts of the Congo it has raged in epidemic form and has killed off large numbers of the population. In other parts of the world sleeping sickness does not occur. A South American form of trypanosomiasis has recently been discovered, but this is in no way similar to the African form.

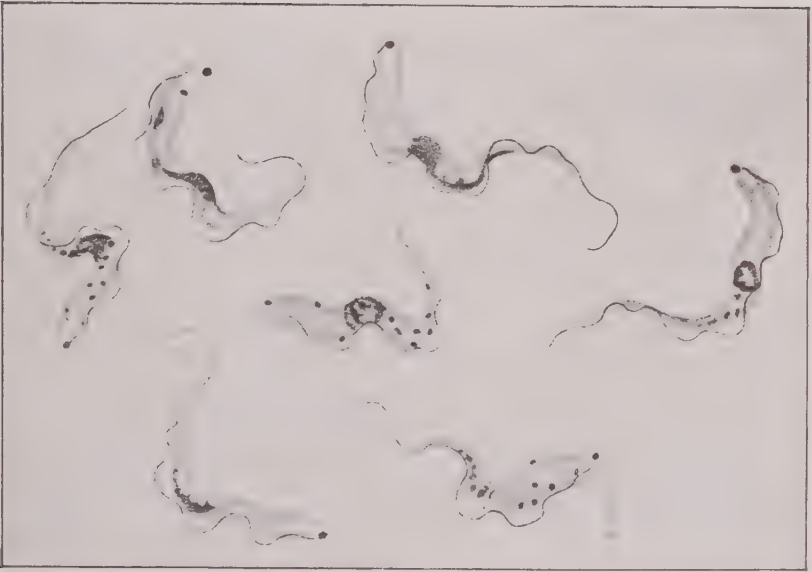
Race.—For a long time it was considered that the disease was confined to negroes. Unhappily, this is not so; Europeans, natives of Persia and India, and other parts are equally liable to it.

Occupation.—Occupations leading people to spend their time in areas where *Glossina palpalis* occurs are dangerous. Hence, fishermen, canoe-

¹ Since this revision was undertaken, reports from Sir David Bruce have arrived from Nyasaland which tend to show that *Trypanosoma rhodesiense* is the same as *Trypanosoma brucei*. In this case the former name must go and the Rhodesian and Nyasaland form of the disease be looked upon as nagana in man.

PLATE X

FIG. 1



Trypanosomes (*T. gambiense*) from the Blood in Sleeping Sickness. $\times 2000$.

FIG. 2



Glossina Palpalis, Rob. ($\times 3\frac{1}{4}$.)

men and the inhabitants of places like the lake shore in Uganda are prone to suffer. These people are half naked and spend much of their time trading and gossiping on the shore, 30 to 80 per cent. of them harboring the trypanosomes in their blood, and being constantly bitten by numerous tsetse-flies. Sex, age, food, health or ill-health have naturally no effect; if the trypanosome is introduced under the skin of the youngest or the healthiest there is no reason to believe that it does not multiply.

Months and Seasons.—As the climate in Central Africa is much the same all the year around it does not appear that the disease is more prevalent at one season than at another.

Description of the Causal Agents—the Trypanosoma Gambiense and Rhodesiense.—The trypanosomes may be demonstrated in the blood, in the cerebrospinal fluid, or in the lymph from lymphatic glands.

1. *In the Blood.*—As a rule the parasites are very scanty here, so it is best to take 10 cc. of blood in a test-tube with a small quantity of sodium citrate solution, and centrifuge this for fifteen minutes. After this the clear liquid is pipetted off and again centrifuged and then the sediment is examined. For bringing out the various details of the parasites in films any of the various modifications of the well-known Romanowsky technique may be employed. Leishman's and Giemsa's methods are especially applicable. The macronucleus appears red, the micronucleus black, the flagellum red, and the basophile granules black, while the protoplasm of the parasite is colored blue.

Plate X, Fig. 1, represents the trypanosomes in the blood of sleeping sickness cases, magnified 2000 diameters, and shows the macronucleus in the centre of the body, the micronucleus at the posterior end; the flagellum taking its origin from the micronucleus, and, running along the margin of the undulating membrane, becomes free at the anterior extremity. A large vacuole is seen near the micronucleus and dots of chromatin are scattered through the protoplasm. Some writers profess to be able to recognize the various species of trypanosomes by their shape and general appearance, but as a matter of fact it is very difficult to distinguish between such trypanosomes as *T. evansi*, *T. brucei*, and *T. gambiense* by microscopic examination alone. The chief morphological distinction between *T. gambiense* and *T. rhodesiense* is the occurrence of posterior nuclear forms (nucleus close to centrosome or even behind it) in the latter when inoculated into rats.

2. *In the Cerebrospinal Fluid.*—In the earlier stages of human trypanosomiasis the trypanosomes are seldom, if ever, found in the cerebrospinal fluid. It is only when the symptoms of sleeping sickness have appeared that they are found with any frequency. Ten to fifteen cubic centimeters of the cerebrospinal fluid are allowed to flow into a test-tube. If any blood escapes with the cerebrospinal fluid the specimen ought to be rejected. The clear, transparent, water-like fluid is then centrifuged for twenty minutes to half an hour, and the sediment examined under a low power. The trypanosomes are seen very readily, there being no red-blood corpuscles and few cells of any kind.

3. *In Enlarged Lymphatic Glands.*—One of the earliest manifestations of trypanosomiasis is an enlargement of the lymphatic glands; all of

these are enlarged—the cervical, axillary, inguinal, femoral, etc. Captain Greig, I. M. S., and Lieutenant Gray, R. A. M. C., made the important observation that the trypanosomes can be demonstrated with great ease in the swollen lymphatic glands, where they seem to be in much greater numbers than in the blood or the cerebrospinal fluid. Greig found that it was only necessary to draw off a drop of fluid by means of a small hypodermic syringe from one of the enlarged cervical glands and to place this fluid under the microscope to find the trypanosomes at once or in a comparatively short time. This is a great advance on the older methods of examining the blood and cerebrospinal fluid, as it used to take, on an average, an hour to find the trypanosomes in the blood of a patient, even when there were five microscopes employed. By examining the glands, however, the trypanosomes may be found in a few minutes.

In What Tissues can the Trypanosoma gambiense and T. rhodesiense be Found?—The trypanosomes are found in much greater numbers in the juice of the glands than in any other of the fluids of the body. From the glands they evidently pass in small numbers into the general circulation, and with it to every part of the body. In the first stages of the disease the trypanosomes are not found in the cerebrospinal fluid. In an examination of many apparently healthy natives who had trypanosomes in their blood, trypanosomes were not found in a single case by lumbar puncture. In the later stage, however, when the symptoms of sleeping sickness supervene, the trypanosomes can, as a rule, be readily found in this fluid in every case of the disease.

Mode of Reproduction of the Trypanosoma gambiense and rhodesiense.—As far as is known up to the present these trypanosomes only reproduce themselves within the human organism by longitudinal division. Other modes of reproduction have been described, but these are not sufficiently definite to warrant acceptance. There can be no doubt that the number of trypanosomes varies greatly from time to time in the blood and fluids. Huge numbers must perish at times and their dead bodies become dissolved in the blood plasma. It is supposed by some that these dead trypanosomes contain a small quantity of toxin which is thus set free in the blood and gives rise to the proliferation of the lymphatic elements, and to the chronic conditions afterward found in the brain and tissues.

Life History of Trypanosoma gambiense and T. rhodesiense outside the Body.—It is evident that as the parasites are only found in the blood and lymphatic fluids of the body, they can only leave it on the escapes of these fluids. There is no evidence that the trypanosome escapes from the body by the intestinal or urinary tracts or by the sweat, salivary, or other secretions. When an animal dies of the disease all the parasites disappear rapidly from the tissues on account of commencing putrefaction. If blood is drawn off during life and kept aseptic it only retains its virulence for four days. Blood dried on threads sometimes retains its infectivity for twenty-four hours, but at the end of forty-eight hours it is inert. If exposed to a temperature of 40° to 44° C. it is slowly killed; 45° C. is rapidly fatal. Trypanosomes, like some bacteria, can be frozen at the temperature of liquid air (−191° C.) for a quarter of an

hour and still retain their vitality. Under artificial conditions, however, Novy and MacNeal¹ have shown that trypanosomes can be cultivated and will live and develop on artificial media outside the body. The culture medium they used was ordinary nutrient agar to which had been added defibrinated rabbits' blood. They first succeeded in growing the rat trypanosome in 1903. Later in the same year they also succeeded in cultivating *Trypanosoma brucei* outside the body. These cultures are, however, by no means so readily obtained as in the case of the rat trypanosome. In this way *T. brucei* has been grown artificially through twenty-three generations, and, so far as the writer knows, is still being grown. *T. gambiense* and *T. rhodesiense* have also been cultivated but with greater difficulty. J. G. Thomson and Sinton state that cultures of the former are more easily obtained than those of the latter. It is to be hoped that the cultivation of the various trypanosomes will assist in the identification of species, as at present their classification is rapidly becoming chaotic. The common way in nature for the trypanosomes leaving the body is by the agency of biting flies. It will be interesting to trace the history of the trypanosome in the interior of one of these flies—the tsetse-fly. The blood along with the trypanosomes is sucked up into the stomach of the fly. Up to forty-six hours one can see living trypanosomes and red-blood corpuscles in the proboscis, and it is possible, especially if the fly is interrupted in its feed, that it may convey the parasites direct to another animal at this time. Afterward it becomes non-infectious and remains so up to the eighteenth day or longer after feeding, when it again becomes infectious. Miss Robertson describes the cycle of development that takes place during this time. If such a fly be dissected, its gut will be found to be swarming with trypanosomes and forms will also be met with in the salivary glands. It would seem that this latter occurrence is necessary before infection of a new host can take place. Miss Robertson believes that the trypanosomes reach the salivary glands by passing up the alimentary tract until they reach the openings of the salivary ducts; they then pass down these to the glands. There does not appear to be a general body infection as is the case with the sporozoites of malaria. Only a small percentage of flies (5 per cent. or so) became infected after sucking the blood of suitable animals. Temperature and other conditions, of which we are at present ignorant, influence this to a marked degree.

How do the Trypanosomes Gain Entrance to the Human Organism?—The answer to this question is by means of the bites of infected *Glossina palpalis* and *Glossina morsitans*. Full descriptions of the tsetse-flies are given in Austen's² monograph, from which the accompanying figure is taken, showing *Glossina palpalis* with artificially outspread wings.

In Uganda, the experiments that were made to find out if this fly

¹ "The Life History of *Trypanosoma Lewisi* and *Trypanosoma Brucei*," *Journal of Infectious Diseases*, November 5, 1904, No. 4, i, 517 to 543; "The Cultivation of *Trypanosoma Brucei*," *Journal of the American Medical Association*, November 21, 1903; *Journal of Infectious Diseases*, January, 1904, No. 1, i, 1; "An Improved Medium for Cultivating *Trypanosoma Brucei*," *Sixth Annual Report of the Michigan Academy of Science*.

² *Monograph of the Tsetse-flies*, Longmans & Co., London.

(*Glossina palpalis*) was capable of carrying infection from the affected to the healthy were as follows: Tsetse-flies contained in small muslin-sided cages were fed on sleeping sickness patients and then, after a certain time had elapsed, on healthy monkeys. We secured the same results as were previously obtained in nagana. Such flies fed on healthy monkeys, were capable of transmitting the disease. But this was not the only proof that these flies could carry the infective agent. On the lake shore there was a large native population among whom we had found about one-third to be harboring trypanosomes in their blood. The tsetse-flies caught on this lake shore, brought to the laboratory in cages and placed straightway on healthy monkeys, gave them the disease, and so furnished a startling proof of the danger of loitering along the lake shore among these infected flies. It is true that the white man runs much less danger than the half-naked native. He is clothed, as a rule, from head to foot, and resents the presence of a biting fly; whereas the natives lie almost naked in the shade of the dense woods which line the shore of the lake and are little affected by the presence of the tsetse-flies.

Are Other Species of Tsetse-Flies besides Glossina Palpalis Capable of Carrying the Infection?—Probably this question must be answered in the affirmative, as Wiggins, experimenting in British East Africa with *Trypanosoma gambiense* and species of tsetse-flies other than *palpalis*, succeeded in infecting healthy from infected animals, and Greig and Gray in Uganda found that *Glossina palpalis* could convey the trypanosoma of a disease, probably nagana, which occurred among cattle, as well as that of sleeping sickness. The carrier of the trypanosomiasis which occurs in Rhodesia and Nyasaland is the *Glossina morsitans*, and in experimental work this fly has also been shown to be capable of transmitting *T. gambiense*. Nagana and some of the other animal trypanosomes seem to be capable of developing in both. Another tsetse, *G. fusca*, may also have to be incriminated. As far as our present knowledge goes all tsetse-flies should be viewed with suspicion.

Do Flies Other than the Glossina Carry the Infection?—The answer to this is, in the writer's opinion, in the negative. Nuttall states that he tried for a long time in England to convey the *Trypanosoma brucei* by means of the genus of biting flies called *Stomoxys*. In no case did he succeed. Greig in Uganda tried the same experiment and failed. In regard to the *Trypanosoma brucei* and nagana, there can be little doubt that it is carried by *Glossina* alone, and the distribution of nagana corresponds with the distribution of the tsetse-fly. So in regard to human trypanosomiasis in Uganda, if the *Trypanosoma gambiense* is only carried by the *Glossina* then the distribution of the fly and the disease should correspond. We set ourselves to work out this problem. Collections of all sorts of biting flies were made from all parts of Uganda, and at the same time the distribution of sleeping sickness was carefully inquired into. In the course of a few months several hundred collections of biting flies were examined. These were divided into two categories, those containing tsetse-flies and those containing other kinds of biting flies but no tsetse. Two maps were taken, one to represent the distribution of *Glossina palpalis*, the other sleeping sickness. When these maps

were completed it could be seen at a glance that the distribution of *Glossina palpalis* and sleeping sickness coincided, and therefore we came to the conclusion that human trypanosomiasis is conveyed from the sick to the healthy by the *Glossina palpalis* and by it alone. Since these observations were made confirmation has come from many different parts of Africa. With the exception of Rhodesia and Nyasaland, where *G. morsitans* acts as the carrier, the rule may be laid down that where sleeping sickness exists so also does *G. palpalis*, the fly being necessary for the transmission of the *T. gambiense* from person to person.

Distribution of the Glossina Palpalis in Uganda.—When it became evident that the *Glossina palpalis* was the only carrier of this infection it was necessary to inquire into its habitat and habits. The results showed that this tsetse-fly is only found on the shore of the lake where there is forest. This forest is thick jungle with high trees and dense undergrowth. The fly is never found on open, sandy beaches backed by grass plains, even although there may be some scrub near the water's edge. It was never found in the grass of the grassy plains, even though the grass was long and tangled. It was not found in banana plantations, and not at any time far from the lake shore. Most of the rivers in Uganda are mere swamps, and up these valleys the fly does not penetrate. The fly is found along the Nile almost as far north as Gondokoro on the border of the Sudan. It also occurs around Albert Nyanza. It is evidently of the highest importance that the exact distribution of this genus should be made out.

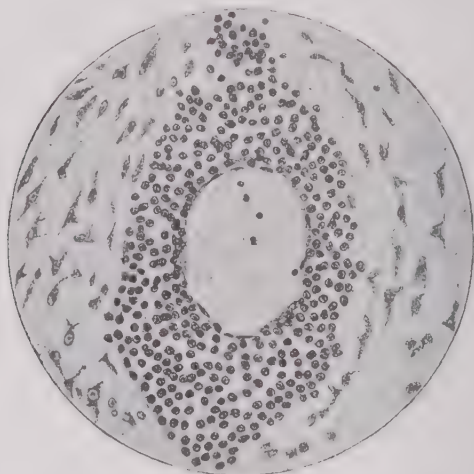
Animals to Which Trypanosoma Gambiense and T. Rhodesiense are Pathogenic.—*T. gambiense* and *T. rhodesiense*, like *T. brucei*, are pathogenic to many species of animals. It is curious that *T. gambiense* and *T. rhodesiense* should include man in their attack, as well as the other animals, whereas *T. brucei*, although, as a rule, much more rapidly fatal and acute in the lower animals, so far as we know, does not attack man unless some of the recent cases in Rhodesia have really been due to this parasite. A supposed case of nagana infection in a laboratory in Italy lends support to such an idea.

Special Pathology.—There is little of special interest to be noted in an uncomplicated case of human trypanosomiasis. The body may be nourished, or extremely emaciated. Bed-sores are often present. The effect of the long chronic toxemia renders the heart muscle flabby and the liver fatty. The lungs and kidneys present nothing abnormal, except the congestion incident to a failing circulation. In a malarious region, naturally, the spleen is generally enlarged, pigmented, and tough. Except then for the constant presence of general enlargement of the lymphatic glands, there is nothing in the naked-eye appearances to proclaim human trypanosomiasis. The lymphatic glands, both superficial and deep, are enlarged. The superficial usually vary in size from a pea to a large bean, and the deep run somewhat larger. Sometimes they increase very much in size, and on section are found to be caseous or to contain collections of pus. This is probably due to some terminal bacterial invasion and not to the trypanosomes. In the brain there is a divergence from the normal and a pathological picture which is fairly

regular. On removing the calvarium, as a rule, a good deal of fluid escapes. The convolutions on the surface of the brain are found to be flattened, and the sulci filled with opaque-looking subarachnoid fluid, giving a ground-glass appearance. The vessels on the surface are injected. On section the brain appears normal, but the lateral ventricles are dilated and contain an excess of fluid. A certain percentage of the cases present much more acute signs of disease. These are the cases in which a terminal bacterial infection has taken place, and the brain may then present all the appearances of acute or purulent meningitis.

Histology.—It is to Mott we owe our knowledge of the pathological histology of sleeping sickness. He states that a definite characteristic appearance is found in sections of the brain, which is found in no other disease. This is a condition of meningo-encephalomyelitis. Throughout the whole central system, but especially in the medulla and at the base of the brain, sections show the pia-arachnoid to be infiltrated with

FIG. 6



mononuclear leukocytes; the inflammation can be traced along the bloodvessels and septa into the substance of the nervous system. The perivascular lymphatics around both large and small vessels are crowded with these lymphocytes. Fig. 6 is taken from his paper, and shows this collection of cells in the perivascular spaces. Similar accumulations are found in the other organs of the body. There is an increase of the mononuclear cells in the blood and the lymphatic glands are enlarged and show a proliferation of their cells. Throughout the body, and especially in those tissues and organs rich in lymphatics, such as the intestine, this proliferation and accumulation can be seen. Human trypanosomiasis is essentially a disease of the lymphatic system, and the irritation and proliferation of the lymphocytes are probably due to a toxin secreted by, or contained in, the bodies of the trypanosomes. The characteristic symptoms are no doubt due to the accumulation of these mononuclear cells in the perivascular spaces of the brain, compressing

the arteries and so interfering with the normal nutrition of the brain cells. The progressive weakness of the body, the tremulous condition of the muscles, the feeble, rapid pulse, the weak voice, and uncertain gait, the rise of temperature, would all be accounted for by this obstruction or interference with the circulation, giving rise to degenerative changes in the nerve cells, and proliferation of the neuroglia.

Terminal Bacterial Invasion.—In certain instances bacterial infections may take place in the late stages and these quickly carry off the already debilitated patient. Streptococci, pneumococci, colon bacilli, and other germs have been described. Pneumonia and purulent meningitis sometimes occur.

Symptoms.—*Effect of Trypanosoma Gambiense on Man—First Stage—Trypanosomiasis.*—When the *T. gambiense* gains entrance into the human organism it begins to multiply and appears in the blood. How long before it appears in the general circulation is, of course, unknown, but in the monkey it usually appears about twenty days after inoculation. The course of the disease is so slow and insidious that months and even years may elapse before any marked signs appear. The first stage, when the trypanosomes are found in the blood but not in the cerebrospinal fluid, may be of a very variable duration. If one may put this into definite figures, it may be said that this so-called stage of trypanosoma fever, this first stage of human trypanosomiasis, may last from three months to three years or more. During this time the native is going about at his ordinary vocation and feels perfectly fit and strong. But there is one outward mark which proclaims the disease and that is the presence of enlarged lymphatic glands. This is a disputed point, but in my opinion this enlargement of the lymphatic glands must be looked on as a constant and early feature. It is not that enlargement of the inguinal or femoral glands should be taken as a sign of human trypanosomiasis; there must be a polyadenitis, and, as a matter of routine, the postcervical glands should be examined first. Every case of sleeping sickness examined by us in Uganda showed this glandular enlargement, and, according to Greig and Gray,¹ the trypanosomes are readily demonstrated on examining the gland juice. Later it was found that the early cases of trypanosomiasis, the so-called trypanosoma or Gambia fever, also, in every case, presented enlargement of the lymphatic glands, and in these active trypanosomes could readily be found. The natives themselves are alive to the fact that when the glands in the neck enlarge, they will, sooner or later, pass into the stage of sleeping sickness, and their custom is then to eat up their live stock, goats, chickens, etc. This enlargement of the cervical glands was used in Uganda to gauge the incidence of the disease in a sleeping sickness area. The result was that in about three-fourths of the population of the islands of Sesse and Kome this symptom was present. As to whether there is any other symptom which can be depended upon to point to the first stage of this disease is a question which, in my opinion, must be answered in the

¹ *Reports of Sleeping Sickness Commission, No. V, Royal Society, Harrison & Sons, St. Martin's Lane, London, 1905.*

negative. Some writers state that there is fever from time to time of an irregular type, but the charts of the men we kept under observation in Uganda showed a normal temperature for several months. The first stage may be dismissed by saying that the blood and lymphatics contain the trypanosomes, and that there is a general enlargement of the lymphatic glands of the body. In Europeans this quiescent stage is not so marked. In a short time after inoculation definite symptoms appear, among which are irregular temperature and in some cases circinate erythematous spots over the body. The spleen also becomes enlarged and eye lesions have been noted.

Second Stage—Sleeping Sickness.—Naturally, in a disease so insidious it is impossible to say with absolute accuracy when the first stage merges into the second. But a time comes when a slight change in the patient's demeanor becomes evident; he is less inclined to exert himself; he lies about more during the day, and at last his intimates see that he has the first symptoms of the disease. When these are well-advanced the expression of the face is sad, heavy, dull-eyed, and apathetic, as is shown in Plate XI, Fig. 1. The body, however, is well nourished, and this is the rule, even up to the time of death, if the patients are well nursed and fed. Complaints of headache or indefinite pains in other parts of the body are often made. The pulse is rapid, shallow and weak, and the heart-sounds faint and distant. The breathing usually presents nothing abnormal. The lymphatic glands are generally enlarged, and vary from the size of a pea to that of a bean. There is nothing abnormal about the skin; it may be at times harsh and rough, but usually is smooth and sleek, and any eruption is quite the exception. The gait is weak, uncertain, and shuffling. There is little strength in the hand grip, and the hands when held out are tremulous. Tremors of the tongue are, as a rule, well-marked. The voice is weak, indistinct, and monotonous. At this time the temperature is usually irregular, often normal in the morning, and rising to 101° or 102° F. in the evenings. During this time the patients in hospital and usually up a great part of the day, sitting in the open air, to the casual observer may show little or no signs of disease. The symptoms gradually increase until after weeks or months the patient is unable to walk, speak, or feed himself. He is then confined to his bed, lying in an absolutely lethargic condition. It is at this time that the sick are often neglected by their friends and become much emaciated. The urine and feces are passed involuntarily. During the last two or three weeks the temperature sinks 6° or 7° below normal, and the patient dies in a state of coma. Plate XI, Fig. 2, represents a case of the emaciated type taken a few days before death.

Nervous System.—The dull, heavy, listless, expressionless, emotionless physiognomy is a marked feature of the disease. Often when a patient is being examined he stares at a fixed point in a vacant way with eyes wide open. The intelligence and memory seem, as a rule, to remain fairly good. Sometimes cases showing mental excitement are seen. In regard to sleep the usual history is that the patients sleep well at night and a good deal during the day. The condition, however, can hardly be called sleep. It is rather a vacant, day-dreaming, apathetic condi-

PLATE XI

FIG. 1



Sleeping Sickness. Second Stage.

FIG. 2



Sleeping Sickness. Shortly before Death.

tion in which the patient remains for hours, often with eyes open, staring unmeaningly at the wall. They can easily be roused by touching or speaking to them. The speech is peculiar, weak, slow, tremulous, and indistinct, sometimes faint and high-pitched, like a whimpering child. When asked a question some little time elapses before the patient answers; he gives, as it were, a sigh, gathers his wits together, and answers with an evident effort. There is nothing, as a rule, noteworthy about the eyes. There is frequently marked tremor of the tongue, lips, and hands, but the tongue alone may be affected. The muscular nutrition is usually good, but power is diminished, as evinced by the grip. Sensibility to touch, temperature, and pain is normal, and the muscular sense is little impaired. In regard to the reflexes, as a rule there is no abnormality. Sometimes, in the early stages, the knee-, elbow-, and wrist-jerks are increased; but in advanced cases the knee-jerks are often diminished and ankle-clonus is in rare cases present to a slight extent.

Alimentary System.—There is little or nothing to be noted here. The appetite is usually good, even in fairly advanced cases. The tongue is moist, flabby, and furred. Inspection of the abdomen seldom reveals anything. There is, as a rule, no enlargement of the liver; the spleen is palpable. The bowels tend to be constipated, and when the patient is bed-ridden, unless care is taken, the colon becomes full of hard scybala.

Circulatory System.—This is more important from a diagnostic point of view, as the heart and pulse tend to become affected early. On auscultation the heart sounds are weak but regular, and there is, in the great majority of cases, no bruit. The pulse is usually accelerated. It has a rate, as a rule, of from about ninety to one hundred or over with a low tension, a small size, easily compressible and regular rhythm.

Respiratory System.—The lungs present nothing abnormal. The breathing is increased in frequency when there is fever, and there is some congestion of the bases in the last few days of life. Pneumonia seems to supervene more frequently in sleeping sickness cases than among the healthy. Dr. Cooke, Kampala, observes that the mortality among the natives from pneumonia has risen greatly since the occurrence of the sleeping sickness epidemic.

Urinary System.—This shows, as a rule, nothing noteworthy.

Cutaneous System.—Sometimes the skin is harsh and rough, and the papillæ prominent, especially over the legs and arms, but in the great majority of cases there is nothing abnormal. In one case an œdematous swelling over the shin was noticed, but, as a rule, swelling, puffiness, and eruptions are conspicuous by their absence.

Lymphatic System.—In every case the superficial lymphatic glands are slightly enlarged, varying, as a rule, from the size of a pea to a bean. They are fairly soft and painless, but in a few cases in the last stages they become inflamed, tender, and break down. This is probably due to a terminal bacterial invasion and not to the trypanosomes. This polyadenitis is considered to be very characteristic and is only found among natives inhabiting the sleeping sickness area. It may be accepted as the most marked symptom of the disease.

Hemopoietic System.—In the early stages the blood may be little altered; later varying degrees of anemia are found. In a certain proportion of cases a polycythemia is seen in the terminal stages with a rise in the percentage of hemoglobin and specific gravity. The cause of this is not clear. The leukocytes are normal or diminished. Just before death a terminal polymorphonuclear leukocytosis, coincident with the final fall of temperature is often noted. The mononuclear cells are relatively increased, the total number of large mononuclears and lymphocytes, generally exceeding 40 per cent. of the total. As Greig and Gray have shown, the cells found in the cerebrospinal fluid are also mononuclear and are increased in number from 23 per cc. in the early stages to 730 per cc. in the fully developed disease. Varying degrees of eosinophilia, generally due to helminthiasis, are also found.

The Temperature Curve.—There is nothing very marked about this in human trypanosomiasis. In the early stage, when the trypanosomes are found in the blood and before symptoms of sleeping sickness appear, the temperature may remain normal. Cases under observation in Entebbe remained without any rise of temperature for six or seven months, and it is impossible to say how long they harbored the parasite before coming under observation. When symptoms of sleeping sickness appear, the temperature, as a rule, becomes irregular, rising to 101° F. or 102° F. in the evening and sinking to normal or slightly below normal in the morning. Other cases occur with the temperature fairly normal throughout the disease, although there is always a certain irregularity. High temperatures may be said never to occur —103° F. being exceptional, and probably due to an attack of malaria. There is one characteristic which is fairly constant: about a fortnight before death the temperature runs rapidly down to 94°, 93°, or even 92° F., and remains so until death. When the temperature becomes subnormal morning and evening, the patient will probably die within a fortnight.

Diagnosis.—From the description of the disease it is seen that it is no easy matter to diagnose human trypanosomiasis in the early stages. All irregular fever resistant to quinine and occurring in people who have lived in a trypanosomiasis area should be viewed with suspicion. In natives there may be no fever and this makes the diagnosis in their cases even more difficult. The pulse should always be examined carefully, as increased rate and low tension are suggestive. The examination of the blood will show a relative mononuclear leukocytosis, which will help to exclude other diseases; and a drop of gland juice, removed by a hypodermic needle from a cervical gland, should show the trypanosomes and so settle the diagnosis. In more advanced cases the peculiar apathetic physiognomy, the pulse, the temperature curve, the tremors of the tongue and hands, the peculiar speech and weak shuffling gait, form a picture which cannot be mistaken for any other disease. But the one unmistakable finding is the presence of the trypanosome in the lymphatic glands, blood, or cerebrospinal fluid, and no medical man should rest content with a diagnosis which does not include the demonstration of the parasite.

Prognosis.—Every patient with human trypanosomiasis who shows symptoms of sleeping sickness dies sooner or later. It is an absolutely

fatal disease. The question has arisen as to whether any of the natives with trypanosomes in their blood are able to kill off the parasite before organic changes in the tissues have been set up and so establish an immunity. This question can now be answered in the affirmative. Greig and Gray remark on this point: "In following the after-history of cases of trypanosoma fever we have arrived at these conclusions: (1) That many of them terminate fatally as sleeping sickness cases, which may be regarded as the usual mode of termination; (2) that a certain number die of intercurrent affections, *e. g.*, pneumonia; (3) that a certain proportion remain well for long periods, indicating that a tolerance toward the parasite has been obtained. It may be said that some of the cases may become in time sufficiently immune to destroy the parasite." The prognosis of human trypanosomiasis even at the present day, with our improved methods of treatment, cannot be said to be hopeful. Taken early a certain number of recoveries may be anticipated, and at the present day a good number of Europeans, who have had trypanosomiasis, are well after the lapse of three to five years or more after the original infection. If some patients have recovered then there is always hope for others, especially in view of improved methods of treatment being discovered. As has been stated, once signs of sleeping sickness develop the case is hopeless. In natives a very great proportion of the trypanosomiasis cases pass into the stage of sleeping sickness and die. The form of the disease in Rhodesia and Nyasaland is extremely virulent and kills those attacked very quickly, generally in a few months. One European lived for over two years but finally succumbed.

Treatment.—Arsenic in some form or other has more influence on the trypanosome than any other drug. Horses, donkeys, and cattle suffering from nagana received 12 to 20 grains of arsenic daily. The result was that in a few days the parasite disappeared altogether from the blood and remained out of it for a long time—from one to five or six months. In every case, sooner or later, the hematozoa crept back into the blood, increased in numbers, and finally killed the animal. In no case was a cure effected. In the most successful case death was delayed for nearly a year. In human trypanosomiasis arsenic, atoxyl, soamin, arsenophenyl, salvarsan, mercury, antimony, and various anilin and other dyes have been tried. Some of these drugs, when given in doses sufficiently large to kill the parasites, produce toxic symptoms, such as optic neuritis and atrophy, and therefore must be used with caution. Intravenous doses of tartar emetic (gr. $\frac{1}{2}$ to $1\frac{1}{2}$, gm. 0.032 to 0.1) have appeared to do good in certain cases. Such a line of treatment, combined with moderate doses of atoxyl (gr. iii to iv, gm. 0.2 to 0.25), is probably the best. Salvarsan (gr. v to vi, gm. 0.4) recently has been reported upon favorably, but it is too soon to judge of its value. Whichever line of drug treatment is adopted it is of the utmost importance to build up the patient's strength in every way possible. It is this part of the treatment that probably accounts for the whites doing so much better than natives.

Prophylaxis.—Since we have found that at present there is no definite and certain cure for this disease, we must consider what means may be devised for its prevention. There are three factors to be considered:

the human host, the parasite, and the tsetse-fly. If this were a disease affecting a species of the lower animals it is evident that the slaughter of all those with parasites in their blood would in all probability nip an epidemic in the bud. The neglect to carry out this measure promptly led to disaster in Mauritius and the Philippines when surra was introduced into these islands. But we are dealing with man. The disease spreads only by means of the tsetse-fly, and in its absence there can be no infection. Is it possible to destroy these flies? They are present in great numbers all around lake shores, where there is dense forest. It has been found that cutting down the bush and clearing the land will get rid of these flies, and much has been done in this line in Uganda, with excellent results. When one comes to Rhodesia and Nyasaland, where *G. morsitans* is concerned, it is quite a different matter, because the distribution of this fly is much more widespread, and its destruction or diminution would seem to be impossible. When once the bionomics of the tsetse-flies are better known some means may be found for destroying their pupæ or attacking the flies in their adult stage. The real crux of the situation as regards prophylaxis lies in the question of the animal or natural carriers of the parasites. When it was discovered in Uganda that the disease was limited to the *Glossina palpalis*, infected areas of the lake shore, the population was moved back into the hinterland away from the fly. It was thought that infected flies would disappear after some years and that then the people could safely return. This was found not to be the case, infected flies still existing even after long periods of time. At first the explanation was not clear, but finally it was discovered that the different wild buck inhabiting the infected zone were harboring the parasites, though showing no sign of the disease, and thus were infecting the flies. Quite recently Kinghorn and Yorke have shown that the same thing holds good in Rhodesia, the wild game acting as the carriers of *T. rhodesiense*. The question therefore arises, Is it possible to destroy the game and so prevent the tsetse-flies becoming infected? The flies without the infection, though a nuisance, are of course harmless. Before any steps are taken in the direction more experimental work is urgently required, and this is now being undertaken by the Commission working in Nyasaland under the charge of Sir David Bruce.

Movements of natives from sleeping sickness areas into non-infected areas must be strictly watched. There is no doubt that the opening up of different parts of Africa by railways, with their increased facilities for travel, has been largely responsible for the spread of the disease into parts where it was previously unknown. If it is necessary to have towns or settlements near river banks or lake shores in palpalis areas much can be done to render these safe by cutting down the jungle in the vicinity and bringing the ground under cultivation. Landing places for canoes and paths through the zone must also be made broad and kept cleared of all bush. As regards personal prophylaxis, there must always be a risk in going into tsetse-fly infected areas. In such cases as much as possible of the face, neck, and hands should be covered, so as to get bitten as little as possible.

CHAPTER V

THE RELAPSING FEVERS

By JOHN L. TODD, M.D.

Synonyms.—English, Relapsing Fever, Famine Fever, Spirillum Fever, Remittent Fever, Recurrent typhus, Tick Fever, Bilious Typhoid; Latin, Febris Recurrens; French, Fièvre Récurrente, Fièvre à Rechutes; German, Typhus Recurrens, Hungerpest, Ruckfallfieber.

Attempts have been made to distinguish several relapsing fevers. It is true that there may be differences in the morphology of the spirochetes, in the symptoms of the diseases which they produce, and in their methods of transmission; but their similarity to one another is so great that it seems wisest to describe relapsing fever as a single disease which may be modified, in various ways, both in its method of transmission and in its course.

Definition.—Relapsing fever is a febrile disease caused by a spirochete and characterized by an intermitting fever; it is transmitted, as a rule, through the agency of a tick or a louse.

Etiology.—In 1868, Obermeyer, in Berlin, saw spirochetes in a patient's blood, but did not publish his observation until 1873, when it was quickly confirmed in many parts of the world. In 1874 Lebert named the parasite *Spirochæta recurrentis*. The work of Carter, in India, and of others proved, by injecting infected blood into healthy persons—as well as by accidental infection at autopsies—that relapsing fever could be reproduced in men by inoculation; it also showed that spirochetes would live and multiply in the blood of monkeys, mice, rats, and, to a less extent, in the blood of other animals. The prevalence of relapsing fever among persons living in crowded, verminous quarters suggested to many (Flügge, Tietin, and Karlinski) that bed-bugs, lice, or fleas might be able to transmit it; but none of the attempts to transmit the disease by their bites has been successful with the exception of one (Nuttall). In this experiment bugs which had partially fed upon an infected animal were allowed to finish their feed on a susceptible one. It has, however, become certain, through the observations of Mackie (1907) and of Sergeant, and Nicholle (1912) and their collaborators, that relapsing fever may be transmitted by infected lice if they are crushed and then rubbed into the scratches. The last named observers also showed that lice hatched from eggs laid by infected lice are themselves infected. In 1904 Ross and Milne found spirochetes in patients suffering from tick fever. Dutton and Todd (1904) made the same observation and showed that the spirochetes could be transmitted by a tick (*Ornithodoros moubata*) and that the infection was carried, through the egg, from one generation of ticks to the next.

Since 1905, when ticks (*Ornithodoros moubata*) infected with *Spirocheta duttoni* were brought to Europe, much work has been done in many laboratories on the African, European, Indian, and American forms of relapsing fever. Novy and Knapp and Breinl and Kinghorn showed that a strong immunity against spirochetes existed in laboratory animals which had recovered from a spirochetal infection; that a partial immunity to reinfection existed in men had already been observed clinically. Dutton and Todd (1907), Breinl, and Carter and Leishman (1909) showed that *S. duttoni*, both in ticks and in men, produce certain granules which, probably, are a stage in the development of the parasite. In 1911 and 1912 it was shown that Ehrlich's salvarsan and neosalvarsan are specifics in the treatment of relapsing fever. In 1912 Noguchi grew spirochetes on a culture medium.

Distribution.—Relapsing fever occurs, or has occurred, in almost every part of the world where men live in verminous squalor. Because the vermin—ticks and lice—which transmit the disease, are distributed by infected men as they travel, relapsing fever is especially likely to appear at points along the main routes followed by the traffic of the world. This has been especially well seen in the introduction of tick fever into Africa; its distribution there marks out the lines of travel followed by the natives of Zanzibar. Though relapsing fever is less prevalent in Europe than it once was, cases are still occasionally seen in Ireland, Norway, and Denmark, and many cases occur annually in Russia, Poland, Southern Austria, and Turkey. Relapsing fever is endemic in many places in the North of Africa and in Asia Minor; tick fever may exist almost anywhere in Central Africa.

Relapsing fever has been described in many parts of Asia; it is endemic in India, in Indo-China, and in parts of China. A fever carried by a tick (not *Ornithodoros moubata*) and probably caused by a spirochete occurs in Persia.

The disease is not endemic in North America, though cases have often been seen in recently arrived immigrants. It has been observed in several places in Central America and it is probably much more widely distributed there and in South America than is recognized at present.

Spirochetes.—The spirochetes are very easily inoculable, and if infected blood or other material be touched they will find their way into the body through the smallest injury to the skin, or even through the unbroken epidermis; consequently, many persons have been accidentally infected in autopsy rooms and in laboratories.

Normally, the spirochetes are transmitted through the agency of an arthropod; ticks do so in many parts of the world. African tick fever is carried by *Ornithodoros moubata*; in Colombia the vector of relapsing fever is *O. turicatus*; the tick fever of Persia, probably a relapsing fever, is transmitted by *Argas persicus*; this tick has been shown, in the laboratory, to be capable of transmitting spirochetes of human origin. *O. savignyi* carries relapsing fever in Abyssinia, and it is possible that *O. tholozani* may do so in India. When the part played by ticks in the transmission of tick fever became known, attempts were renewed to transmit other forms of relapsing fever by the bites of the vermin

infesting the populations among whom these diseases existed. Animals infected with various spirochetes of human origin were subjected to the bites of bed-bugs, fleas, head lice, and body lice. After an interval of a varying number of days the vermin were allowed to feed upon healthy, susceptible animals. None of them became infected as they would have done had the ticks which transmit relapsing fever been allowed to feed upon them in the same way. Only once have spirochetes been transmitted by the bites of bed-bugs; in that instance the infection was probably carried mechanically on the mouth parts of the bugs which were partially fed on an infected animal and then allowed to finish their meal on a healthy one (Nuttall). Examination of lice and bugs fed upon infected animals showed that spirochetes could live in the alimentary canal of bugs and lice long after the feeding at which they were ingested; moreover, it was proved, by inoculating them into susceptible animals, that these spirochetes were infective. It has been shown, also, that susceptible animals and men become infected if lice, *Pediculus corporis* and *P. capitis*, which have previously fed upon blood containing spirochetes, are crushed and their bodies rubbed into scratches, such as those which are made by lousy persons in scratching themselves. It is probable that this is a usual method of acquiring the disease.

Long-known peculiarities of the distribution of relapsing fever are easily understood when it is known that it can be transmitted by lice. During epidemics of relapsing fever in Russia, those, often young men, who frequent vermin-infected, public night-refuges are very likely to contract the disease. In an Indian epidemic among school children very many more boys than girls were attacked; the boys were much the more lousy. Doctors and nurses in relapsing fever hospitals rarely contract the disease, while those who come in contact with the patients before they are cleansed, or if they are wearing their soiled clothing, may become infected.

It was assumed, at first, that the ticks transmitted the spirochetes by their bites. At present, it is uncertain whether they do so; for it is possible for them to transmit infection in another way. Soon after an *Ornithodoros moubata* or an *Argas persicus* commences to feed, it excretes a considerable quantity of clear fluid, which is probably derived from the blood ingested; the fluid issues from the coxal glands, which are placed just behind the first pair of legs. Sometimes a small amount of thick, whitish excrement is passed at the same time by the anus. A fair amount of the clear coxal fluid, often 0.1 cc., may be voided by a large tick; it dilutes the thick anal excretion and the mixed excretions run between the tick and the host on which it is feeding so that both are well smeared with them. Active, living spirochetes have been found in the mixed fluids, and it is quite conceivable that these organisms, as well as the coccoid stages of the spirochetes—which are said to be found in both the coxal fluid and in the anal excretion—may pierce the skin or find their way to the wounds made by the mouth parts of the ticks, and so infect the animal fed upon. Some assert that the bites of infective ticks will not infect susceptible animals unless they void excreta while they feed; this is denied by Marchoux and Couvy (1912)

for *Argas persicus* and *Spirochæta gallinarum*. Certainly, this method of infection, though it is not necessarily the only one they possess, makes the ticks quite capable of transmitting the disease.

The progeny of an infected tick are infected and capable of transmitting spirochetes for, at least, three generations; lice hatched from eggs produced by infected parents are also infective. An infected tick may retain its infectivity for an indefinite period even although it feeds only on uninfected persons; nevertheless, not every tick is infective; it is said that ticks may become immune to spirochetes and that it is then impossible to make them infective by feeding them on infected blood.

The spirochete, *Spirochæta duttoni*, which causes African tick fever, has been studied with more minuteness than any of the spirochetes causing other forms of relapsing fever. A description of its morphology and development will serve, in main part, for all of the pathogenic, blood-inhabiting spirochetes of man. This spirochete is a filiform organism, measuring about 14μ to 20μ in length and 0.2μ in width; it is said to be slightly broader than the spirochetes of European relapsing fever. Its body is disposed in a number of waves so that it has the appearance of a spiral thread—hence its name; but if fresh and stained preparations are carefully examined it will be seen that the spirochete is more like a ribbon than a thread, since its cross-section is flattened, and that it is not a true spiral, since its waves lie practically in one plane. It is actively motile, and progresses, with either end foremost, both by lashing movements of the whole parasite and by a “corkscrew motion” in which the waves of the parasite move along its body and the whole parasite rotates along its longitudinal axis. Two, or several, spirochetes may be joined together end to end and in very heavily infected blood they may agglomerate in huge clumps or in hair-like tresses. In fresh preparations the substance of the spirochetes is usually homogeneous and it is difficult to distinguish the details of their structure. By appropriate methods of preparation and by using the highest magnifications it is seen that a spirochete consists of a thin outer coating, or periblast, and of a central core. The periblast stains pink by Romanowsky’s method, or its modifications, while the core stains in a deep purple color resembling that taken by chromatin. Usually this chromatinic core is unbroken, but, not infrequently there is a small break in it which appears as an unstained spot in the spirochete. When it exists this spot occurs most often at the junction of the central with a terminal third of the spirochete. The periblast may be effiliated at either extremity and it may extend for some distance beyond the end of the core; this affiliation has sometimes been described as a terminal flagellum. There are no lateral flagella. In many spirochetes appearances may be seen, by careful examination, which suggest that a very fine and narrow undulating membrane is wound spirally about them; but it is uncertain whether such a membrane exists. Although spirochetes may multiply in the peripheral blood by splitting longitudinally they usually divide transversely. Transverse division occurs at those thinner portions of a chain of spirochetes, joined end to end, which seem to consist of periblast only. Spirochetes which are about to divide transversely are longer

than usual, those dividing longitudinally are thicker; so that, for these reasons alone, there may be a good deal of variation in the morphology of the spirochetes in a single preparation. The chromatinic cores of spirochetes taken from the blood of persons who are near the crisis of an attack are especially liable to be fragmented into several rod-like or granular masses; spirochetes with large granules attached to them either laterally or terminally, or with terminal club-shaped swellings, are not uncommon in blood examined at this time.

Spirochetes coiled up in a compact skein are occasionally seen in the blood; they are common in smears made from the organ juices—liver, spleen—of infected animals. Coiled spirochetes are especially numerous in the organs of subjects which have died just before the spirochetes have disappeared from the peripheral blood at the crisis of an attack. The chromatin of coiled spirochetes is usually, but not always, fragmented. Spirochetes, whether coiled and fragmented or not, are often found within endothelial cells in various organs and within phagocytes in the circulating blood. Rarely, and especially in the organs, they are seen within red blood cells.

If blood taken from the alimentary canal of a tick which has fed some time previously on an infected animal be examined, some of the spirochetes contained in it will be normal in appearance; the chromatinic core of others will be much fragmented and many will be coiled in skeins. Often, the coiled spirochetes are enclosed in a lightly staining matrix; similar forms may be seen in films made from the organs of infected animals. The chromatinic material of a spirochete, coiled and encysted in this way, may be disposed irregularly in short rods or granules, within the matrix, so that it is difficult to recognize that they result from the fragmentation of a spirochete. Spirochetes altered in this way and normal in appearance may be found within the alimentary canal and Malpighian tubules and oviducts of an infected tick. They may also occur within the cells of these organs, or in the connective tissue and muscle (Wolbach, 1913).

It is uncertain whether granules formed in this way are the result of a degenerative or of a regenerative process; but it is very possible that they, and perhaps the larger terminal and lateral granules, which are sometimes attached to the spirochetes, may be infective. They are said to multiply by division. They occur in the ova and in the coxal and anal excretions, and it has been suggested that the infectivity of these fluids and of young ticks, hatched from the eggs of infected parents, may be due, in part at least, to them. Similar granules have been seen in the spirochetes of fowls, and fragmentation of the chromatinic core frequently occurs in several other spirochetes; that both are common occurrences seems an additional reason for believing that both may be developmental processes.

The morphology of the spirochete, as described, is that which can be observed in preparations which have been dried, fixed in alcohol, and stained by a modification of the Romanowsky method. It is mentioned with full appreciation that complete significance cannot be attached to observations made on preparations prepared in this way until they

have been controlled by the examination of fresh material and of preparations made by more perfect methods.

Some authors state that the spirochetes of relapsing fever are filterable and they suggest that the coccoid forms, described above, may be concerned with the production of the filterable form of the spirochete; nevertheless, it is very doubtful whether any stage of these spirochetes can be said to be filterable in the usual sense of that term.

The spirochetes (*S. gallinarum*) of fowls, ducks, and geese, and other birds causes a fatal disease in them; it is transmitted by a tick (*Argas persicus*). Apparently non-pathogenic spirochetes have been found in the blood of cattle, bats, rats, mice, and fish; the way in which they are transmitted is not known. Spirochetes are often associated, usually in the tropics, with the presence of chronic or acute ulcerations of the skin, and at least two spirochetes are frequently parasites about the teeth of men in all parts of the world. All of these, with *Treponema pallidum*, and many free-living, non-pathogenic organisms, are closely allied, by their morphology, with the spirochetes of relapsing fever. Consequently, the spirochetes form a widespread and very important group of organisms. Spirochetes, other than those of the relapsing fevers, have been mentioned because a study of them has often revealed facts which have added to our knowledge of *S. recurrentis*.

There has been much discussion concerning the systematic position of the spirochetes and, especially, whether they are to be classed with the protozoa, with the bacteria, or in a third kingdom distinct from either of these. The question is not yet decided, but at present the weight of opinion is that they should be placed near the bacteria.

Attempts have been made to distinguish several species among the spirochetes which cause relapsing fevers. These attempts have been made because of slight differences in morphology and pathogenicity for men and animals and because of numerous experiments in which animals refractory to one spirochete are shown to be immune to others. The attempts to distinguish species by slight differences in length, or by the number of waves in their bodies, are absurd, since slight variations in size may occur in a single species and the number of waves in a spirochete depends, largely, upon the way in which the preparation containing it has been made. Although there may be differences in the pathogenicity of different spirochetes and in the immunity resulting from infections, the most useful view to take, at present, is that these differences are only sufficient to constitute variations of a single species, *Spirochæta recurrentis*, and that this spirochete may be transmitted by various blood-sucking arthropods. From a practical point of view it would be useless to distinguish several relapsing fevers when the symptoms, treatment, and prophylaxis of all are practically identical.

The Vectors.—Bed-bugs have transmitted spirochetes experimentally from infected to healthy animals, but the usual carriers are ticks and lice. Ticks¹ belong to the order *Acarina*; they and other members of

¹ *Ticks: A Monograph of the Ixodoidea*, by Nuttall, Warburton, Cooper, and Robinson, University Press, Cambridge, is a very complete work.

this order transmit other diseases besides those caused by spirochetes. Ticks of various species and habits are parasitic on men, and on other mammals, birds, and reptiles in all parts of the world. The ticks which transmit pathogenic spirochetes belong to the family of the *Argasidae*, which have no scutum, their mouth parts are not conspicuous when they are looked at from above, and their habits are not like those of other ticks but resemble those of a bed-bug.

It has been said already that *Argas persicus* transmits *Spirochæta gallinarum*; it is also the vector of a human tick fever, of unknown causation, in Persia; and it probably transmits relapsing fever in India. Ticks of this genus have no eyes. They are oval in shape and brownish red in color. They are frequently found about chickens in parts of the southern United States.

In Africa, *Ornithodoros moubata* is the vector of tick fever. During the day this tick remains hidden in the cracks and crannies of a native hut or in the sand of its earthen floor. At night it comes out, finds its way, probably by smell, to those sleeping in the hut and sucks blood from them. Its bite causes little irritation. Usually, it is nothing more than a wheal, rather smaller than that caused by a mosquito's bite, with an obvious wound, surrounded by a zone of ecchymosis at its centre. If a tick is disturbed it sometimes tries to escape, but usually it feigns death. A tick may feed for two or three hours before being satisfied and then it is so distended that its skin is quite smooth instead of wrinkled as it was when feeding commenced. Although the ticks will feed almost every fortnight, if they are given an opportunity of doing so, they can live for six months without food.

Lice have six legs; they are, therefore, insects. There is a distinct louse for almost every animal; their distribution is universal. The body louse and the head louse may be vectors of *Spirochæta recurrentis*.

Pathology.—There is usually some jaundice and there may be petechiæ, submucous in the mouth, and subserous in various organs; but the most striking feature is a great increase in the size of the liver, and especially of the spleen. The spleen is soft, congested, and hyperplastic. All of the organs are hyperemic and the marrow of the long bones may be red. There is often marked cloudy swelling of all the organs, and there may be fatty degeneration of the heart, liver, and kidneys. Similar changes are seen in experimental animals; in sections of tissue taken from them, and stained appropriately, spirochetes can often be seen lying within the endothelial cells. In the spleen and liver, especially, fragmented and unfragmented spirochetes are often found within phagocytes.

Symptoms.—The length of the incubation period may vary between two and twelve days; the first attack usually commences in less than seven days after an accidental infection. There are often indefinite prodromes, malaise, headache, unusual perspiration, for a day or two before the onset. This is usually sudden; there are pains of the muscles and in the back, characteristic, intense pain in the long bones, and headache. The temperature rises rapidly, sometimes with a chill, to 103° or 104° F. or even higher. With the fever is a pulse of 115 or

more, rapid breathing, thirst, flushed and tender skin. The tongue is coated, anorexia is complete, and there is often slight nausea and vomiting. There may be either constipation or diarrhœa, or both in succession. The temperature remains high, with slight morning remissions, until from the fourth to the seventh day, when it falls by crisis within a few hours to normal or below; if often remains subnormal for a few days after the attack. A very profuse perspiration accompanies the crisis. Although the attack leaves the patient weak he feels wonderfully well. A sudden death from heart failure may occur at the crisis in elderly patients and in those who are weak. During the attack the spleen and liver are enlarged, often painful and tender. The patient's skin becomes yellowish, and there may be a macular eruption; occasionally there are submucous pectechiæ in the mouth. Both hemoglobin and red cells are reduced, and there is a polymorphonuclear leukocytosis. The urine is diminished and is often albuminous. Epistaxis, herpes, hiccough, iritis, and retinitis may be complications. Delirium is often seen in severe attacks; meningitis and paralysis are rare occurrences. Pneumonia and bronchitis are not infrequent.

During the interval the spleen and liver diminish in size, the patient's strength returns rapidly, he feels well, and is confident that there will be no recurrence. But in about eight days from the crisis there is almost always a second attack of fever, usually less severe than the first, but with the same symptoms. There may be from three to six, or even seven, attacks of fever, with intervening periods of apyrexia, before the illness ends. In the European form of the disease there are rarely more than two febrile periods. In fatal cases there may be no fall in the temperature and the spirochetes may increase steadily in numbers until the patient dies of toxemia. As a rule, pregnant women abort and deliver a still-born child. This description will do for all of the relapsing fevers, though there are differences between them. For example, in the European form of the disease both pyrexial and apyrexial periods are rather longer than they are in the African.

During the attack the spirochetes can be found in the blood in increasing numbers. As a rule, the more severe the attack the more numerous the spirochetes; but they are said to be less numerous in African tick fever than in other relapsing fevers. With the crisis they disappear from it; but a very prolonged search will reveal them in peripheral blood taken during the interval and a susceptible animal can be infected by the inoculation of blood drawn from a patient at that time. The usual fate of the myriads of spirochetes circulating in the blood at the crisis is not known completely. Many of them become encysted in the cells of the liver, spleen, and lungs; others are engulfed by phagocytes.

The nature of the mechanism by which spirochetes produce the symptoms of relapsing fever is uncertain; but they are probably caused by a toxin produced by the spirochetes. It is unknown whether the recurrent course of the fever is due merely to periodical accumulations of such a toxin or, as is the case in malaria, to the repetition of some causative event in the developmental cycle of the parasite. If the attacks are caused by the first alternative the spirochetes may disappear

because of the production of antibodies by the patient; the second alternative explains at once both febrile attacks and disappearance of the spirochetes.

Immunity.—An immunity results from an attack but its degree varies and persons may be twice infected in a single winter. Africans who live in a tick-infested region often suffer so little from relapsing fever that they declare the ticks to be harmless; but natives who go to that region from districts where there are no ticks, contract tick fever at once. It is suggested that the immunity of natives who are constantly exposed to tick bites may be maintained by frequent reinfection.

Prognosis.—The disease is not a serious one if it occurs in strong persons who are well cared for, but the mortality in some epidemics may be large; because, as its method of transmission makes clear, it is especially liable to occur among miserable and ill-cared-for persons whose power of resistance is small. The death-rate, under the old methods of treatment, in strong, well-cared for patients, was about 2 per cent.; but under adverse conditions, might reach from 10 per cent. to even 50 per cent. In fatal cases a secondary infection is often the immediate cause of death, but death may result from the toxemia of an intense infection or from collapse after a crisis. In well-nursed persons, properly treated by modern methods, the mortality should be negligible.

Diagnosis.—An absolute diagnosis depends upon the demonstration of spirochetes; they must be seen under the microscope. Although they may be easily seen, if they are numerous, in a fresh preparation, they are best found if they are rare, by the examination of a thick, dehemoglobinized film of blood. A large drop of blood is placed upon a slide and smeared over an area of about 1 cm. square. The blood is allowed to dry and the preparation is then dehemoglobinized in water and fixed in absolute alcohol; or it may be dehemoglobinized and fixed in one operation by placing it in 90 per cent. alcohol, to which hydrochloric acid has been added, in the proportion of 1 drop to 5 cc., and then washing it in running water to free it from acid. After drying, the preparation is stained by any nuclear stain. Carbol fuchsin or methylene blue will do; but the best is one of the modifications of Romanowsky's method, such as Giemsa's. One of the best modifications of this stain, if large numbers of slides are to be stained, is that recommended by Christophers and Stephens. A Romanowsky stain should be used because other parasites, such as that of malaria, which might be in the blood, are well stained by it.

All of the hemoglobin has been removed from slides prepared in this way, and the red cells become unstainable, so that, in a well-made preparation, nothing is seen but the nuclei of the white cells, a small amount of debris, perhaps a few basophilic red cells, the blood platelets, and any parasites that may be present. Malarial parasites, as well as spirochetes, are well shown by this method.

It may happen that spirochetes cannot be found in this way in a patient who is examined during an apyrexial period. In that event a drop of blood from the suspected case should be mixed with a drop of

blood containing spirochetes taken from an infected person. The mixed blood is placed on a slide under a cover-slip, ringed with paraffin to prevent evaporation, and placed in an incubator at 37° C. After half an hour, when the preparation is examined, the spirochetes should be clumped together if the suspected patient has relapsing fever (Löwenthal).

If there is any difficulty in finding the spirochetes, at least 25 cm. of blood should be taken from a vein, mixed with sodium citrate solution to prevent the blood from coagulating, and injected into a young rat or into a monkey. Blood taken from the animal inoculated should be carefully examined twice daily for ten days before assuming that it has not become infected. If none of these methods of diagnosis can be employed, the clinical course of the disease, with its characteristic, relapsing fever, will be sufficient to justify a diagnosis.

It must be remembered that relapsing fever may easily be complicated by other diseases; the method by which it is transmitted is proof that those suffering from it have been living under unsanitary conditions. In the tropics, relapsing fever is often mistaken for malaria. In instances where a diagnosis is attempted without a microscope, the coincidence of a natural fall of temperature at the crisis is sometimes accepted as a "therapeutic proof" that the fever, for which quinine had been given, was malarial.

Treatment.—This, like that of syphilis, has been revolutionized by the discovery of salvarsan. Before it was discovered, the treatment of relapsing fever was entirely symptomatic. Baths and sponging were used to reduce high temperatures. Phenacetin and aspirin or opium were given for headaches and boneaches, and purges were prescribed on general principles. Strychnine, ether, and other stimulants may be useful in cases of collapse; elderly or weak patients should be cautioned against exciting themselves after a crisis.

Several unsuccessful attempts have been made to utilize the marked immunity, which can be acquired against spirochetes, in producing a serum which might be used in the treatment of the disease.

A host of observers, in all parts of the world, have agreed that Ehrlich's salvarsan is a specific in the treatment of experimental and clinical infections by *Spirocheta recurrentis*, *sensu latiore*. On experimental grounds, it has been suggested that the best time for administering salvarsan is just before the crisis; there is no proof that it is so. The drug is best given intravenously in doses of 0.2 to 0.25 gm. to persons of average weight; it is efficacious, though much less satisfactory, if it be given subcutaneously, and it has been given by the rectum in children. The spirochetes disappear and the temperature falls within twelve hours after the drug is injected. Ill effects, such as vomiting and a rise in temperature, may follow treatment. Relapses after treatment occur in a small proportion (9 per cent.) of the cases treated; but recovery is usually uninterrupted and strength and a normal blood count are quickly regained. If a relapse does occur a dose of 0.15 gm. of salvarsan controls it. Neosalvarsan is probably just as efficient and a much safer remedy than salvarsan, though its action may be rather slower. The dose intravenously is 1 to 1.45 gm. to a person of average weight. Atoxyl

and tartar emetic, valuable in the treatment of trypanosomiasis, have little effect on relapsing fever.

The way in which the drug acts on the spirochetes is uncertain; but it has been suggested, since the granular debris of destroyed spirochetes have been found in the liver and spleen cells of cured animals, that the organism may play an important part by assisting in the destruction of spirochetes.

Prophylaxis.—Attempts to control any of the diseases transmitted by an invertebrate host may be directed primarily against the parasite causing the disease or against the vector which transmits it. Salvarsan and neosalvarsan are such efficient destroyers of spirochetes that relapsing fevers may be expected to disappear from areas where these drugs are persistently used in the treatment of the disease. Infected persons should be given neosalvarsan as soon as possible in order to destroy the spirochetes in them. They should be cleansed and isolated, so that vermin may have no opportunity of feeding upon them, nor of passing from them to healthy persons. The clothing of infected persons should be sterilized, and beds and rooms, occupied by them, should be very thoroughly disinfected in order to destroy all vermin. During an epidemic those who have been in contact with cases should be freed from vermin in order that they may not infect ecto-parasites, should they have been infected, before the disease declares itself in them; they should also be watched carefully so that cases may be isolated and treated at the earliest moment possible.

Those who live in localities where relapsing fever exists should take every precaution to avoid being bitten by ticks, bugs, and lice. In Africa, the ticks have been found on the veldt and on a wild pig; but, as a rule, they are only found in camping places and in houses frequented by natives. Such places should be avoided; it is much safer to clear a space and camp in the bush.

It is possible to infect animals of several species with each variety of *Spirochæta recurrentis*; but no instance has been recorded in which animals have been found to be naturally infected. Consequently, it is not necessary at present, as it is in the prevention of trypanosomiasis, to institute measures for the destruction of animal reservoirs from which the invertebrate transmitters of relapsing fever might become infected.

It is unknown whether spirochetes survive from one epidemic of relapsing fever to the next in a free form, in animal hosts, in invertebrate hosts—lice and ticks—in which the spirochetes may be transmitted from generation to generation, or in men—either in occasional, atypical cases which escape recognition or as harmless, tolerated parasites.

CHAPTER VI

SYPHILIS

By WILLIAM OSLER, M.D.

AND

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Synonyms.—Lues Venera, Bad Disorder, Pox, Morbus Gallicus; French, Verole; German, Lustseuche, Krankheit der Franzosen; Italian, Siflide; Spanish, Sifilis; Swedish, Radezyge.

Definition.—Syphilis is an infectious disease, acquired by contagion or transmitted by inheritance, which runs a chronic course and exhibits local and general constitutional manifestations. Its signs and symptoms are protean, but they are often exhibited in a determinate order, on the basis of which several distinct clinical stages are recognized. The lesion produced is an infectious granuloma, similar to that seen in tuberculosis and leprosy.

Etiology.—The story of the search for the cause of syphilis is a tale to make the judicious grieve. "One hundred and twenty-five causes of syphilis," said Lassar, speaking in 1905, "have been established during the last twenty-five years." The idea of a living contagium as the cause of syphilis is of course an old one. The story of its "discovery" began in the seventeenth century with the finding, by Kircher (1658) and Abercromby, of a contagium animatum (vermiculi); and it continued almost without interruption until the last chapter was written by Schaudinn and Hoffmann. Of some historical importance was the announcement by Lustgarten, in 1884, of the discovery of a characteristic bacillus, which created interest and aroused discussion; but it was later shown that the organism seen in the internal organs was probably the tubercle bacillus, and the one found in genital chancres, the smegma bacillus.

The Spirochæta Pallida, or Treponema Pallidum.—It was in 1905 that the final word on this subject was spoken by two German investigators.¹ On May 17 of that year the paper of Schaudinn and Hoffmann was read before the Berlin Medical Society. It was a model of calmness; and despite the conviction which they must have had that they had got "to the quick of the ulcer," they presented the facts quite simply and left etiological deductions to others. They had found, they said, a characteristic organism in syphilitic lesions; it was readily told from other similar bacterial forms and had been present in the primary sore

¹ The early articles of Schaudinn and Hoffmann appeared in the *Arbeiten aus dem Kaiserl. Gesundheitsamt*, Band xxii, Heft 2, S. 527, and in the *Deutsche med. Wochenschr.*, 1905, Nr. 18, S. 711

of 7 cases examined, in the anal papules of 1 case, in the genital papules of 8, in 2 closed primary lesions of the skin of the penis, in inguinal buboes in 12 cases, and once in the splenic blood. Almost immediately corroboratory reports were coming in. By December, 1905, the *Spirochæta pallida* had been found by various observers all over the world in a great variety of syphilitic lesions. The vast amount of work subsequently done has tended only to confirm these early findings both as to the presence of the *Spirochæta pallida* in luetic lesions and as to its absence elsewhere.

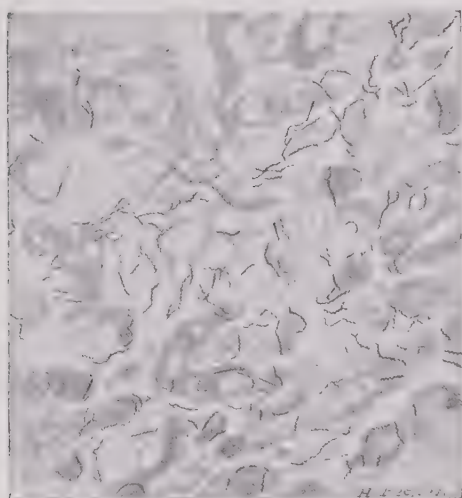
The *Spirochæta pallida* or *Treponema pallidum* (Plate I, Fig. 1) is a long, delicate, non-refractile, spirally curved organism. It was first studied with very high magnifications (1200 to 2800), but it may be seen quite well with the ordinary oil-immersion lens. Its average length is from 4 to 14 μ ; smaller forms, 2 to 3 μ in length, are also seen, and organisms 20 μ long have been observed. It is pointed at both ends. Its spirals are sharp, clear cut, tight and corkscrew-like, and are less definite toward the ends than elsewhere. They vary in number from six to twenty-six, but shorter forms with only two or three curves are also seen. The length of each spiral measures from $\frac{4}{5}$ to 1 $\frac{2}{3}$ μ , and the large number of spirals in proportion to the length of the organism is a characteristic feature. The whole organism is usually somewhat curved; it may be S- or C-shaped, and occasionally forms a closed circle.¹ It is circular in cross-section. In both stained and fresh specimens flagella have been seen, usually one at either end, although occasionally more. The flagella are extremely delicate and are about as long as four to six spirals of the organism. The motility is of three kinds: rotation on the long axis, snaky, whip-like undulations of the whole body without locomotion, and forward and backward movements. The motion persists, if physiological salt solution be added, for six hours; it is stopped by glycerin, and gradually disappears on exposure to the air. Certain observers have been able to see in the organism nothing more than Brownian movements. Unlike other spirilla, the *Spirochæta pallida* retains its spiral form when at rest. The presence of a surrounding undulating membrane seems probable; Schaudinn claimed to have observed it best in specimens stained by the Loeffler method for flagella.

When examined with an ultramicroscope, bodies suggestive of nuclei have been seen, but the presence of a nucleus is not beyond doubt. The organism probably multiplies, like the trypanosomes, by longitudinal fission; no signs of transverse division have been observed. It does not bear spores. In smear specimens the *Spirochæta pallida* usually lies free and is seldom enclosed in a cell. It is, however, frequently in intimate relation with a red-blood cell, often touching it with one end and not infrequently embracing it. The organisms may lie separate from one another; but often they lie in groups, and occasionally they form definite tangles. Their life history is not known; what have been described as involution forms are occasionally seen. Ross has recently observed inclusion bodies within the blood cells, which are

¹ This picture is probably caused by two C-shaped organisms in apposition.

interpreted as stages in the life history. Schaudinn regarded certain of the oval and spindle-shaped forms as resting stages. One of the marked characteristics of the organism is its tinctorial obstinacy. No stain colors it deeply and many do not color it at all. It does not stain by Gram's method. In sections of chancres the *Spirochæta pallida* lies in the epithelial layers of the epidermis, in the lymph spaces, and in the thickened vessel walls. According to Levaditi it is first seen free within the vessels; thence it passes to the endothelium, where it causes the swelling and occlusion characteristic of the pathological picture of the disease. It is seen in greatest number in sections of organs from children dead of congenital syphilis; in these cases the tissues may literally swarm with the organism (Fig. 7). Most authors hold that the *Spirochæta pallida* is carried by the blood-stream. Its modification and final disappearance from a lesion during specific treatment have

FIG. 7

Section of lung, congenital syphilis, $\times 800$.

been frequently observed; but similar observations have been made during the spontaneous healing of chancres, and it is not definitely established that the treatment (whether local or general) is responsible for the disappearance of the organism.

Method of Obtaining the Organism.—To examine a chancre for the *Spirochæta pallida* the surface should first be well cleansed with soap and water, rinsed and dried. It is important that this be done with care, for thorough cleansing removes large numbers of the *Spirochæta refringens*, the organism usually present on the surface of sores, and, from its similarity with the *S. pallida*, offering difficulties in the micro-

scopic diagnosis. The lesion should then be lightly curetted and the slight oozing checked by pressure with a piece of gauze. After any blood still present has been wiped away, the sore is then squeezed between the fingers until a drop of blood-tinged serum exudes. This may be examined by dark-field illumination, or a thin smear preparation may be made from it. If the chancre be covered with epithelium one can either remove the covering mechanically or obtain a drop of serum by aspiration. Enlarged lymph glands may be easily examined by withdrawing a drop of serum from them with an ordinary small aspirating syringe. Serum for smears may be obtained from lesions of the exanthemata by scraping off the covering epidermis. Certain observers have recommended the formation of artificial blisters by vesicants and examination of the serum obtained from them by aspiration. For examination

of the blood the method of Noeggerath and Staehelin is best: 1 cc. of blood is removed and mixed with 10 cc. of $\frac{1}{3}$ per cent. acetic acid. The mixture is centrifugalized and thin smears are made from the sediment.

Staining the Organism.—It is of first importance that the staining and examination be promptly done; for the organism stains badly, and sometimes not at all, in smears that are not perfectly fresh, and the color after staining gradually fades. The smear may be well-fixed by simple air drying. Fixation by the vapor of osmic acid is said to give good definition and to bring out the tapering extremities particularly well; this may be readily accomplished by placing the specimens for a few seconds over the mouth of a bottle containing osmic acid crystals.

Staining methods are almost as numerous as the investigators. On the whole, the modification of Giemsa's method, recommended from the first by Schaudinn and Hoffmann, is probably the best, although it is time-consuming. According to the technique originally advised, the specimen is placed, after fixation, in freshly prepared Giemsa's azur-eosin¹ and allowed to stay twenty-four hours. It is then washed with water and examined. At present a slight modification of this method is widely used. The Giemsa stain now used is known as "Giemsa-Lösung für die Romanowsky-Färbung," and may be obtained from Grüber in Leipzig, and has the following formula:

Azur II-eosin	3.0 gm.
Azur II	0.8 mg
Glycerin (Merck, c. p.)	250.0 gm.
Methyl alcohol (Kahlbaum I)	250.0 gm

The specimen is dried in the air and hardened in absolute alcohol for one hour. The stain is then diluted with distilled water (1 drop of stain to 1 cc. of water), a fresh dilution being made for each examination. In this diluted stain the specimen is allowed to remain for twenty-four hours. Good results may be obtained if the stain stay on for only half an hour, but they are not quite so certain. In this stain the *Spirochæta pallida* is colored a delicate violet purple. The nuclei of the leukocytes should be colored a deep blackish red; if this is not the case the specimen has not been properly stained. Probably not all the organisms take up the stain, for they are not as numerous in a stained specimen as in a hanging drop from the same source. Many other staining methods have given good results, particularly various other modifications of the Romanowsky stain. A good specimen may be simply obtained by staining the smear with liquid India ink. For demonstrating the organism in sections the best method is that of Levaditi; it is a modification of the technique of Ramón y Cajal used for nerve fibres.

Cultivation of the Organisms.—The *Spirochæta pallida* may now be grown in pure culture. The media devised by Noguchi consists of serum-water to which a piece of sterile rabbit kidney or testicle has been added. Cultivation is carried out under strict anaërobiosis. Noguchi succeeded

¹ Following is the formula:

Giemsa's eosin (2.5 cc. 1 per cent. eosin to 500 cc. water)	12 parts
Azur I (1 to 1000 water solution)	3 parts
Azur II (0.8 to 1000 water solution)	3 parts

in reproducing the disease in animals by injecting the organisms cultivated in this way. By a special technique he has also succeeded in obtaining cultures in a fluid medium, consisting of ascitic fluid alone or mixed with bouillon.

Diagnosis.—The *Spirochæta pallida* is probably but one member of a large group of organisms with similar morphology, and it offers therefore some difficulties in microscopic identification. The chief trouble is caused by the *Spirochæta refringens*, for this is found just where the *pallida* is likely to be sought for. It occurs in the mouth, on the tonsils, in ulcerating lesions, in smegma, and on venereal warts. The *Spirochæta pallida* can, however, usually be recognized by its delicacy, its slight refractility, its tinctorial obstinacy, and by the number and tight, corkscrew configuration of its spirals. The *refringens* (Plate XII, Fig. 2), on the other hand, is larger, thicker, more refractile, and quite easily and deeply stained; but most characteristic of all are its spirals, which are broad and wavy or undulating, rather than corkscrew-shaped. Its ends are rarely pointed and often blunt, its movements are more rapid than those of the *Spirochæta pallida*, and it occurs in great numbers in smear specimens. Not more than 2 or 3 of Schaudinn's spirochetæ, on the other hand, are usually seen in one field of a smear from a chancre; and often they are much less numerous. A number of different non-syphilitic spirochetes have been described by Noguchi, some of which (notably *S. microdentium* and *S. mucosa*) closely resemble *S. pallida* in morphology.

Classification.—There is still dispute as to the classification of the *Spirochæta pallida*. Schaudinn regarded it as a protozoan, distinguished from the other spirochetes, on the one hand, by its preformed spiral morphology and by its possession of flagella, and from the spirillæ, on the other hand, by the flexibility of its spirals, by the possession of only one flagellum at either end and by its apparent capacity for longitudinal fission. He agreed with Vuillemin's suggestion that the organism be called a *Spirochæta*.

Significance.—1. Experts are almost unanimous in regarding the specificity of this organism as a "probability bordering on certainty." The very extensive and careful scrutiny to which the *Spirochæta pallida* has been subjected, although it has brought out confirmatory observations in great number, has failed to reveal a single well-established fact at variance with the idea that this organism is really the cause of lues.

2. The *Spirochæta pallida* occurs almost constantly in primary and secondary luetic lesions. Failures to find it date largely from the period before the technique was developed or the eyes trained; and the growing experience throughout the world is that the organism of Schaudinn and Hoffmann will be found in chancres if carefully and persistently looked for.

3. The *Spirochæta pallida* occurs unmixed with other organisms in the depths of primary and secondary luetic lesions, and in the blood.

4. It is in the most contagious syphilitic lesions (the chancre, the condyloma, and the mucous patch) that the *Spirochæta pallida* is most often found and in greatest number.

PLATE XII

FIG. 1



Spirochæta Pallida. Smear from Hard Chancre.
Giemsa's stain. $\times 1000$

FIG. 2



Spirochæta Refringens. Smear from Chancroid. $\times 1000$.

5. The *Spirochæta pallida* occurs in the internal organs, the specific exanthemata, and in the blood of congenitally syphilitic children. It is also found in the placenta and in the umbilical cord, and the absence of other organisms in these situations is a striking fact.

6. The *Spirochæta pallida* is absent from non-luetic lesions.

7. The *Spirochæta pallida* disappears under treatment which cures syphilis.

8. The *Spirochæta pallida* is less numerous in healing sores than in others.

9. The *Spirochæta pallida* does not pass through a Ton-filter. This fact is rendered striking by the observations of Metchnikoff and Klingmüller that the syphilitic virus behaves similarly.

10. The *Spirochæta pallida* has been a frequent, although not an absolutely constant, finding in the experimental syphilis of apes, not only after inoculation from human cases, but also in the disease transmitted from one animal to another. Its absence from the normal skin of the ape has been established by Kraus.

11. Cultivation of the organism and experimental reproduction of the disease by injection of pure cultures, practically completes the chain of evidence as to the causal relation of the *Spirochæta pallida* to syphilis.

The value of the *Spirochæta pallida* from a diagnostic standpoint is established. Its almost constant presence in chancres and absence in non-luetic lesions is beyond dispute; and we are therefore justified, in the event of a positive microscopic finding, in making a positive diagnosis of syphilis and in instituting treatment on this evidence alone. If a single examination be negative we are not justified in regarding the lesion as non-luetic, just as we would be without justification in regarding a sputum as non-tuberculous after examining one smear preparation.

General Pathology.—Syphilis, which begins its pathological existence as a modest, inactive Hunterian chancre, soon enters upon a career that is unsurpassed for the variety of its manifestations. There is no organ in the body,¹ nor any tissue in the organs, which syphilis does not invade; and it is therefore manifestly difficult to speak, at least at all concisely, of the pathology; just as it is almost impossible to describe its clinical symptoms without mentioning almost every symptom of every disease known. Certain general pathological features are, however, characteristic, and these must be here described: the other more specific changes will be treated under affections of special organs. One notices throughout the pathological changes of lues the cellular infiltration and the prominent part taken by the bloodvessels, both of which features play such an important rôle in the chancre. Virchow, indeed, called attention to the fact that all the syphilitic lesions from the chancre to the gumma are granulomata so much alike that they cannot be differentiated.

1. **The Syphiloma.**—The following are the features of the general pathological anatomy of the syphiloma as outlined by Jullien:

“(a) Infiltration of the derma and the mucous layers with small cells. These cells, which closely resemble the aspect of embryonic elements

¹ The prostate is a possible exception. A few cases of supposed syphilitic prostatitis were collected by Fournier from the literature, but none of them was regarded as convincing.

encountered in fleshy granulations, are heaped up at the periphery of the vessels, between the trabeculae of the corium, and finally involve the papillae and Malpighian bodies to such a degree that the limitation between these two layers of the skin entirely disappears.

“(b) The inevitable destruction of those cells which are incapable of organization. At the end of a certain time the infiltrate undergoes a fatty degeneration and enters into the organism by resorption or ends in a purulent dissolution. In any case the vitality of the secondary syphiloma is not sufficient to transform it into definite tissue. After its disappearance the elements of the tissues in the midst of which it was established again take on their normal disposition without any necessary loss of substance.

“(c) The centrifugal course of the neoplasm, both in its development and in its retrogression. It is always from the centre to the periphery that the infiltration takes place; the borders of the lesion are consequently more recent than the centre; hence the differences in aspect which may be presented in the two parts. When the centre becomes depressed under the influence of retrogression, the neoplasm may maintain its maximum of development at the borders; this is the reason for certain forms (cup-shaped, annular, etc.).”

The pathological changes explain the features of the various lesions. “The papule,” for example, “is prominent because there is cellular infiltration; hard, because this infiltration is dense; it is brilliant, because the epidermis is tense over the summit; surrounded by a collarette, because the coloring matter of the blood furnishes an extravasation; and, finally, when resorption takes place, the epidermis wrinkles at its surface and is eliminated by an ephemeral desquamation.”

2. **The Cutaneous Syphilides.**—These cannot be treated in detail on account of their multitudinous varieties. The pathology, however, of the macule, the papule, and the pustule will suffice as examples of the characteristic changes. The *macule* consists of an exudation of leukocytes and plasma cells about the small vessels, a proliferation of connective tissue, an infiltration of the hair, sweat, and sebaceous follicles, with round and plasma cells. Horny pigment cells are occasionally deposited in the papillae (Ehrmann's melanoblasts). The *papule* represents a further development of the macule, due to an advance in cell proliferation toward the surface and toward the depth. Plasma cells and leukocytes occur in groups (“Zellenwucherungen”), often about the ducts of sweat glands. Round cells are numerous and giant cells frequent. Exudation of leukocytes and transudation of serum into the epidermis may occur and the papule may, therefore, be accompanied by a pustule or vesicle. The *pustule* presents a similar picture except that supuration is present at the mouth of hair follicles or sebaceous glands. The walls of vessels, hair follicles, sebaceous and sweat glands show cellular proliferation and infiltration of cells, which reaches to the horny layer, obliterating the distinction between rete and cutis.

3. **The Gumma.**—This lesion belongs to the infectious granulomata and shows no specific elements or structure. The pathological changes are similar to those of the papule, but destructive changes are present

and give the lesion its character. There is softening of the connective tissue, which is transformed into a thready, mucoid mass, consisting of detritus and cells which have undergone fatty degeneration. Lymphoid, pus, and epithelioid cells are present. At first there are no new blood-vessels formed, but later these become a feature. The overlying epidermis becomes inflamed and the upper layers of the corium swollen with a semiliquid infiltration. The gumma may be surrounded by dense, sclerotic, scar tissue, and present undeniable histological analogies with tubercle. The gumma, however, may be absorbed and finally disappear without degeneration or ulceration; this is a remarkable characteristic and is well illustrated in gumma of the testicle. The gummatous change may be diffuse, rather than confined to the limits of an infectious granuloma. The microscopic distinction between gumma and tubercle is always difficult and often impossible. In general, epithelioid cells are more frequent in tubercle, fibroblasts and connective-tissue strands in gumma; in gumma, caseation and connective-tissue proliferation are simultaneous, in tubercle the latter succeeds caseation; gummatous caseation is a much slower process than tuberculous caseation; the tubercle is often free from vessels, but new-formed vessels are a prominent feature of gumma and often persist even during necrosis. Giant cells are certainly more characteristic of tubercle than of gumma.

When the growth of the gumma ceases the younger peripheral cells become organized into connective-tissue cells, forming an envelope for the cheesy and gummatous nucleus. This envelope shrinks, the semi-fluid portions are absorbed, and finally a scar (possibly calcareous) is left behind.

4. Lesions of the Mucous Membrane.—When the papule occurs on mucous membranes or on moist portions of the skin it presents certain other pathological characteristics, but remains essentially a papule. Cell proliferation invades the cutis, necrosis of the surface occurs, and a characteristic deposit is formed. This is removed mechanically and is again replaced; or else the papillæ proliferate and mechanical stimulation leads to great hypertrophy, immense cauliflower condylomata resulting.

5. Inflammations.—Syphilis may determine inflammatory changes. Arteritis and peri-arteritis have already been referred to; pharyngitis is frequent; acute nephritis is not rare; iritis and periostitis are common, and in the lungs a chronic fibroid change is sometime seen (the fibrous interstitial pneumonia of Virchow). The non-specific inflammation of the viscera which occurs in tertiary syphilis commences as a congestion and runs a subacute or chronic course. It ends in new connective-tissue formation, cirrhosis of the organ affected, and atrophy of its parenchyma. Later the inflammation is gummatous in character.

6. The Blood.—The blood picture, which is never characteristic, may vary from that of chlorosis to that of pernicious anemia. A normal count, although unusual, occurs. A severe chlorotic anemia is the rule in the primary stage and is most marked in women. With the appearance of the rash there is further diminution in the hemoglobin; the red blood count may remain about where it was or drop very rapidly. In

tertiary and hereditary syphilis the picture may be that of primary pernicious anemia with numerous megaloblasts; normoblasts, gigantoblasts, microcytes, and poikilocytes are also seen. Mercurial treatment causes the red cells to rise, although its *first* effect is often a drop, accompanied, in some cases, by hemoglobinuria. Sometimes a hypercythemia results from the treatment; but if it be continued too long or in too large doses, mercury itself may cause an anemia. A large inunction or injection of mercury, given after the disease has ceased to be local and has invaded the lymph glands, causes an immediate drop of from 10 to 20 per cent. in hemoglobin, which rises, in a few days, to normal or above normal. This is known as Justus' test; it may be obtained in any case of florid lues, is not present during the early primary stage, and, while not certainly pathognomonic, is valuable.

The leukocytes are normal in the primary stage, or slightly increased. If mercury be given, the percentage of polymorphonuclear neutrophils increases. During the secondaries there is slight leukocytosis, with increased lymphocytes and eosinophiles. The severe anemia of the tertiary stage is often accompanied by leukocytosis with high lymphocytosis, and myelocytes occur in severe cases.

7. Amyloid Degeneration.—Syphilis plays an important role in the etiology of amyloid degeneration; 21 per cent. of 80 cases of amyloid degeneration studied by Hoffmann in the Berlin Pathological Institute were due to syphilis. The intestines, liver, spleen, and kidneys are oftenest involved; and the condition is common in association with rectal lues in women. It is rare in the congenital form.

The Nature of the Syphilitic Virus. Acquired syphilis is transmitted only by contact, either direct (venereal, buccal, mammal, corporeal) or mediate (the various contacts of domestic, social, industrial, and professional life). Hereditary transmission may be paternal, maternal (the mother actually passing on her own infection to the product of conception, or else transmitting the disease from a luetic semen without herself receiving apparent infection), or from both parents.

The virus possesses the power of remaining dormant for a long time and suddenly arousing into activity again. It circulates in the blood, and exists in the sperm, whence it may pass to posterity. The father is, indeed, most often responsible for hereditary syphilis, but he may beget a healthy child, although himself in the acute stages of the disease; and not all congenital lues is paternal in origin, for a woman with acquired syphilis is liable to bear infected children. So long as the disease is in the primary or secondary stage it is intensely contagious; in general, the virulence decreases with the duration of the illness, and at some period of its life its contagiousness ceases. Just when this occurs no one can say; there is not even agreement as to the contagiousness of the tertiary lesion,¹ but clinical evidence goes to show that on the average a well-treated case of syphilis offers no danger of direct transmission after three years have elapsed without symptoms. The danger, however,

¹ The discovery of the spirochete of Schaudinn in tertiary lesions probably settles this dispute. Neisser and others have recently proved, by experimental inoculation of apes, that the gumma is infectious.

of transmission to posterity lasts much longer—how long it is impossible to say.

The virus is certainly contained in the primary and the secondary lesions, and most abundantly in those that are secreting or degenerating. Whether the normal secretions contain it is not definitely agreed. Diday, Pardova, and others, working on the tears, milk, sweat, and urine, failed to demonstrate the presence of the virus by inoculations; Fenger, however, apparently proved that the secretions possess contagious properties when inoculated in sufficient dose. The virus rapidly loses its activity outside the human body; Boeck found that when dried upon linen it soon became no longer infectious. The virus cannot apparently enter the body except through injured skin or mucosa.

The facts as to luetic immunity can perhaps be best stated in an itemized way, but one has always to bear in mind that no statement about syphilis is always and absolutely true, and that even such well-founded generalizations as Colles' law contemplate only a majority, although in this case it is the vast majority, of clinical observations.

1. Syphilis is exclusively an affliction of the human race.
2. In human beings there is *no absolute* immunity to the disease.
3. Syphilis does, however, confer a certain degree of immunity, and its occurrence in an individual renders a second attack quite unlikely, although not impossible.

4. There is a certain degree of natural immunity to the disease. The occurrence of syphilis, for instance, in only one of several individuals exposed to exactly the same source of infection is a fairly frequent clinical observation difficult to explain in any other way.

5. Syphilis is essentially a disease acquired in youth, and, although no age is immune, the initial sore rarely occurs after the fiftieth year. Habits of life would, of course, account for this fact; whether immunity also plays a rôle it is impossible to say; but the proverb of Ricord should at least be kept in mind: "Let him who lusts after syphilis make use of his youth, for in old age its acquaintance cannot be first made."

6. There seems to be good ground for believing that the existence of syphilis in a community for some length of time results in a relative immunity to it, as expressed by a lessened severity of its symptoms. This observation was strikingly made after the great European pandemic; it has been repeated since, when the disease, freshly introduced into a community and taking on a virulent form, has gradually become milder; but there is no reason to suppose that this immunity will ever become absolute and that the disease will, of itself, "die out."

7. **Colles' Law.**—Colles was the first to propound the generalization; but the law was first formulated by Beaumès, and may be thus briefly stated: A woman who has borne a syphilitic child is immune to syphilis, although she may present no signs of the disease.

8. **Profeta's Immunity.**—When a woman suffering from syphilis in its contagious stage bears a child which shows no taint, the child may be suckled by its mother with impunity and will not contract the disease from her. This fact was first stated by Behrend, but was repeated by Profeta, whose name has since been coupled with it. It should be borne

in mind that immunity of this sort is only transferred while the mother is suffering from active syphilis; the law cannot be extended to include all the offspring of a luetic mother. This immunity may be only an apparent one in the sense that the child has received a true but latent infection; this is the view Diday and others have upheld in order to explain late hereditary syphilis.

9. When syphilis is inherited it is usually the eldest child which suffers most, and often it is the firstborn only.

10. When a woman is infected with syphilis after conception, the child is apparently often immune. It may, however, be born syphilitic, and placental transmission is a well-recognized fact.

11. The question of the transmission of syphilis to the third generation is not settled beyond all dispute. Cases of pronounced congenital syphilis have been met with in the children of healthy parents; but the existence of a cured acquired syphilis in the parents can seldom be absolutely excluded. Many of the reported cases do not bear careful scrutiny and transmission of syphilis to the third generation, if it takes place at all, is certainly not a common occurrence. Fournier is, however, strongly of the opinion that heredosyphilis may have the same harmful effect on the fetus as acquired syphilis; in the same way as the latter, it constitutes a predisposing cause for abortions, stillbirths, and the early death of infants.

Clinical Features.—Three clinical stages in the course of a typical case of syphilis were recognized by Ricord, and to these others have added a fourth. The primary is the stage of the chancre; the secondary is the stage of the acute general invasion of the virus; the tertiary is the stage of the late, relatively non-virulent, localized manifestations, and the quaternary is the stage of what were termed parasymphilitic phenomena. The division is, of course, more or less an academic one; no disease, syphilis least of all, follows any rule in its clinical phenomena. Nor is the evolution of the disease so constant or orderly an affair as this classification might suggest. One of the stages may be entirely absent; the secondary and tertiary stages may be separated by long intervals or be almost simultaneous, and almost any variation may be observed. On the average it represents an approximation to the truth; and while its limitations must be constantly kept in mind, its value both in clinical observation and in facilitating description cannot be questioned.

The Chancre (*Synonyms:* Infectious, Indurated, or Hunterian Chancre; Initial Sclerosis).—Syphilis makes its debut in the guise of the Hunterian, or hard, chancre, which appears as a rule within the first three weeks after infection, rarely earlier than the tenth day. Attention is sometimes first called to the lesion, as Hunter observed, by an itching in the affected part; but the sore, both at its onset and later, is usually quite painless and free from sensitiveness on pressure. Its very early appearance varies greatly and at this time diagnosis is often quite impossible. "In the early part of my life," wrote Colles, "I thought I could tell what was a chancre; but I am now convinced that a primary venereal ulcer may begin in any one possible form of an ulcer." Usually it is a small papule

which is first noticed. As the sore develops, however, it takes on more or less diagnostic characteristics. It forms a brownish-red, firm, often button-like nodule with a shallow surface depression. Its size, shape, and consistency vary greatly; but characteristically it is circular or oval, measures 1 x 1.5 cm., and is quite hard. Its edges are sharply defined and the induration about it does not, as is usual in other inflammations, extend far beyond the limits of the lesion itself, but terminates abruptly. Its extreme mobility is a characteristic feature. At this stage the chancre is really an exulceration resting on an indurated base. The surface of the base is regular, brilliant red (much the color of muscle), and on a level with the surrounding tissues or slightly above them. Its centre is not infrequently grayish or diphtheroid. The secretion is scanty and thin, and suppuration does not usually occur. If the lesion is on a mucous membrane, the surface remains moist and glistening; but in chancre of the skin the secretion often dries and forms crusts. Secretion may, however, be altogether absent. The induration, which may feel like parchment, is usually more resistant and elastic, resembling cartilage. The sore is typically single, *but in about one-fourth of the cases it is multiple*; Fournier has reported a patient exhibiting twenty-six simultaneous initial lesions.

The chancre is usually accompanied by no general constitutional disturbances. Involvement of the neighboring lymph channels, particularly along the dorsum of the penis, is seen, but it is not associated with inflammatory redness. Soon after the appearance of the chancre the neighboring lymph glands become enlarged, forming, when the sore is a genital one, the characteristic luetic inguinal buboes, most frequently seen in both groins. They remain discrete, are hard, free from tenderness, and do not suppurate. They survive the chancre and become, later, part of the general adenopathy of the secondary stage. Enlarged inguinal glands are occasionally entirely absent.

Complications.—1. The chancre is sometimes accompanied by marked inflammatory reaction. This often takes the form of intense edema and phimosis. A condition of elephantiasis may be present and gangrene is occasionally seen.

2. Not infrequently the chancre becomes phagedenic. This is most often seen in old men and in diabetic or otherwise diseased patients.

3. The Hunterian chancre may be accompanied by a soft chancre, and this mixed infection is frequently seen in large dispensaries. Very often, too, the evolution of a soft chancre into a hard one is observed. This is, of course, due to a mixed original inoculation; the soft sore, with a short incubation period, appears first, its base becomes gradually indurated and soon takes on the typical Hunterian characteristics (mixed chancre).

Site.—Chancres may be either genital or extragenital. About 8 of the latter are seen to 90 or 100 of the former. The characteristics of the lesion vary with its site, and induration is usually less marked in chancres of the skin than of the glans, and in women than in men.

(a) *Genital Chancres.*—The primary lesion is usually situated on the genitals. In men it is most frequently seen, as Hunter observed, on the

frenum and coronal sulcus; but the glans, the urethra (as far as the fossa navicularis), the dorsum of the penis, and the scrotum are occasionally the site of chancre. In women it may occur anywhere on the external genitalia, and even in the cervical canal itself. Perigenital chancres are seen on the mons veneris, the inner surface of the thighs, and the perineum.

(b) *Extragenital Chancres*.—The contagion of syphilis, although usually spread by normal sexual intercourse, is not necessarily so transmitted; and the primary lesion is by no means always found on the genitalia. In certain regions of Russia, for example, where there are no physicians and where the most wretched hygienic conditions prevail, syphilis is, according to Tarnovsky, in 70 per cent. of the cases transmitted by extragenital contagion. In these districts there are few prostitutes, and "rural syphilis in Russia is first and foremost syphilis of the innocent."

Perverted intercourse may account for extragenital chancres; so, too, may certain of the contacts of every-day life (contagion from drinking cups, kissing, barbers' utensils, etc.). More frequent, however, are the extragenital sores acquired by the special contact of physicians; and obstetricians and gynecologists run a particular risk in this respect. Chancres have been transmitted by surgical instruments; the Eustachian tube has been infected by a catheter; the disease has been transferred from one patient to another on a silver-nitrate stick; vaccination and tattooing have spread it; and in the Continental countries the industry of wet-nursing is a well-recognized source of contamination. Extragenital chancres are, therefore, often innocently acquired (*syphilis insontium*). They occur about the lips, on the nose, chin, brow, cheeks, eyelids, and conjunctivæ; on the gums, the tonsils, and at other sites within the buccal cavity; on the fingers, most often of nurses and physicians; on the breasts; and, rarely, on the extremities.

Varieties.—Chancres vary as to the extent and form of ulceration (simple fissures, small ulcers, giant ulcers), the depth of ulceration (erosive, ulcerative, and boring chancres), the characters of the surface (papular, squamous, diphtheroid, pustular, and papillomatous chancres), and the character of the base (foliaceous, parchment, hypertrophic, elevated, and elephantiac chancres).

Course.—With the appearance of the eruption retrogressive changes in the chancre itself usually begin; they may set in earlier or be much delayed. The induration diminishes, the central portions of the chancre undergo fatty or ulcerative degeneration, and finally the sore disappears. Absolutely no trace of the lesion whatever may be left behind, particularly if it be situated on a mucous surface. As a rule an indurated scar persists and may last for years; not infrequently the scar is pigmented. If the sore becomes infected or assumes a phagedenic character its clinical course is obviously altered. Prognosis as to the severity of the syphilis is by no means to be made from the character of the sore.

Diagnosis.—The sharply defined borders, the induration, the slight sensitiveness, the scanty, non-purulent secretion, and the motility are the typical clinical features of the Hunterian chancre; but no one of

them is invariable and the diagnosis of the sore is usually difficult, very often impossible, and, as a rule, not to be made, aside from finding the *Spirochæta pallida* microscopically, until sufficient time has elapsed for the appearance of secondary symptoms. The chancroidal ulcer and the lesions of herpes progenitalis offer the greatest difficulties in diagnosis of genital chancre. Other genital lesions which may be confused with chancre are ulcerating secondary syphilides, suppurative folliculitis, erosive balanitis and vulvitis, and certain of the tertiary syphilitic lesions. The appearance of these is, however, usually not typical of Hunterian chancre; the history is often helpful; and microscopic examination of smears will eliminate the non-luetic lesions.

One can hardly overemphasize the importance of keeping a patient with a genital sore under observation, for it is very difficult indeed, positively, to exclude syphilis in these cases. Many of the diagnostic rules are fallacious; the idea, for instance, that chancroidal lesions are always multiple, luetic lesions always single, has led many astray. Little value can be attached to the history in these cases and therefore the incubation period of the sore cannot often be determined with accuracy. Nor does the absence of induration exclude chancre.

The diagnosis of extragenital chancres offers greater difficulties. Here the position of the lesion instead of attracting one's attention immediately to syphilis may throw one off one's guard. The characteristics of the Hunterian sore are, however, usually to be found, and one should look particularly for the accompanying adenopathy. Chancres of the skin may be mistaken for pustular ecthyma and for tuberculous ulcerations. In the pharynx one may suspect diphtheria; on the fingers, lips, tongue, and tonsil differentiation from carcinoma is often difficult. Extragenital chancres may also resemble ordinary inflammations (*e. g.*, paronychia, abscess of the tonsil, etc.).

Prognosis.—In itself the chancre is usually benign; if ulcerative or phagedenic in character, however, it may in itself be a grave affection by reason of its effect on general health and of the loss of substance which it brings about. In certain situations its nature is more serious; urethral chancres, for example, lead to stricture and nasal chancres to atresia of the nostrils. The supposed increased gravity of extragenital chancres is probably due to other factors than the intrinsic nature of the lesion itself (*e. g.*, mistaken diagnosis and insufficient treatment, accompanying secondary infection, etc.).

The Secondary Stage.—The initial lesion is the clinical expression of syphilis in its primary and localized form. We do not know that the infecting agent has actually remained at the site of original inoculation or in the lymphatic glands nearby; what we *do* know is that during the first few weeks of the disease (the so-called second incubation period) no manifestations other than the local one are to be observed. After a lapse, however, of about four to eight weeks from the appearance of the chancre the disease changes rather suddenly from a local to a general one; constitutional signs and symptoms, in great variety, appear; and this appearance marks the onset of the secondary stage of the disease. To this stage no terminal limit can be set; sometimes it lasts a few weeks,

at other times many months; its course is greatly influenced by treatment; and if the disease is not well treated it may either pass directly into the tertiary form or disappear entirely, to reappear, after the lapse of months or years, as tertiary syphilis.

The symptoms of secondary syphilis are in a general way those of a more or less grave acute infection; but a large and motley group of specific symptoms is also superadded. The most characteristic of the latter are the lesions of the skin and mucous membranes; these are also quite often the most apparent manifestations as well as the first to appear.

Symptoms of an Acute General Infection.—*General constitutional disturbances* are usually present, often marked and in striking contrast to the feeling of well-being during the primary stage. There is loss of weight and strength; the patients feel badly, and this condition may be exaggerated by anxiety over the disease. The appetite becomes poor, extreme anorexia being occasionally observed. In nervous women, however, bulimia is sometimes seen. Headache is a frequent, characteristic, and troublesome symptom. Usually it is described as a deep heaviness present most of the time, but much worse in the evening. Sometimes it is violent, almost intolerable, and quite prevents participation in the activities of life. The tonsils are often swollen independently of the occurrence of mucous patches. Sore throat is frequently complained of (angina erythematosa syphilitica). When the angina spreads to the uvula and soft palate the picture is characteristic and almost pathognomonic. The inflamed area itself is dark crimson, and is abruptly separated from the healthy mucosa anteriorly by an absolutely sharp border. The lingual tonsils may be swollen and dysphagia result. The spleen is sometimes enlarged, and this fact, if fever and roseola suggest typhoid fever, may add confusion to the diagnosis. Occasionally jaundice is present. Albuminuria is not frequent, but a form of nephritis occurs, which will be discussed under Visceral Lesions. Anemia is a feature of the secondary stage; it is usually of the chlorotic type and may be attended by definite clinical symptoms (cardiac palpitation, sense of oppression, etc.). In neurotic individuals syphilis often causes an extreme exaggeration of the symptoms previously present. Intense psychic depression is not at all rare; pains in the limbs and analgesias and anesthesias (particularly of the breasts in females) are seen, and sometimes the patients suffer from definite convulsive attacks. The patella reflex may be abolished.

Enlargement of the lymphatic glands is one of the characteristic features of secondary syphilis. It is not a local affair, but an expression of general infection. The glands are not large, are indolent, painless, hard, discrete, unaccompanied by neighboring lymphangitis, and do not suppurate. The intensity of the glandular involvement is not proportional to the severity of the disease; on the contrary, marked glandular swelling usually accompanies mild lues, and *vice versa*. The most frequent lymphatic glands to be involved, arranged in order of predilection, are the post-cervical, the sternomastoid, the submaxillary, the epitrochlear, the axillary, and the inguinal. Enlargement of the epitrochlears is particularly suggestive, since its involvement in other conditions is not very

frequent. Involvement of a small gland just under the outer border of the pectoralis major has been considered almost pathognomonic of lues; the gland is certainly rarely involved in cases of acute infectious processes, since it lies off the drainage tract of parts oftenest so affected. Recently, however, such an enlarged gland was removed for diagnosis and found to be tuberculous. Enlargement of the inguinal glands is of little diagnostic value; it is by no means always seen in syphilis, and is often seen in other conditions. Palpable and even enlarged lymphatic glands in this region are, indeed, almost a constant finding in patients seen in a genito-urinary out-patient clinic, and Dietrich has found that out of 499 healthy individuals 99 per cent. showed enlarged lymph glands somewhere in the body.

Fever.—Fever is a frequent phenomenon of the secondary stage and is one of the features of its resemblance to an acute infectious disease. At the end of the fifteenth and during the early years of the sixteenth centuries, when syphilis assumed epidemic proportions, it was compared with smallpox (owing probably to the intensity and persistence of the cutaneous features), and hence the name *variola magna*, the great pox, or *the pox*. The frequency of fever during the course of syphilis is variously estimated. A large majority of cases have a slight elevation of temperature in the period of incubation. Throughout its course the disease may be afebrile, and patients with the most extensive lesions may have normal temperature.

The fever occurs at three periods—preliminary, stage of invasion, and at any time during the tertiary lesions:

1. *Preliminary Fever.*—During the period of incubation the patient may be without symptoms, but there may be a feeling of weakness and loss of appetite, with pallor. In a few instances at this period fever occurs. It may be ushered in by a chill (Lang) and be accompanied by headache, nausea, and pains in the limbs.

2. *Fever of Invasion.*—As a rule, by the time we see the patient in hospital the fever has disappeared. Various estimates give the proportion of cases with fever at from 25 to 35 per cent. It is probable, if we had accurate measurements, that slight fever would be found in a much larger proportion. It may antedate the eruption by a week or two and may set in abruptly with a chill. It is commonly associated with headache, malaise, and a furred tongue. The type of fever is usually remittent. Where malaria prevails the case may be confounded with the estivo-autumnal type of this disease. Much less frequently the fever of invasion is frankly intermittent. No case of this type at this period of the disease has come under our observation, but Fournier refers to it. The pains in the limbs and about the joints, with the slight fever, may lead to the diagnosis of rheumatic fever. At this stage the picture may occasionally simulate typhoid fever; Fournier describes the condition as "*typhose syphilitique*."

3. *Fever of the Tertiary Lesions.*—It is particularly at this period that fever may lead to serious errors in diagnosis. The profession scarcely realizes that protracted fever of almost any type may occur in tertiary syphilis. It is probable that many of the cases of obscure, unclassifiable

fevers which are described from time to time are due to latent syphilitic lesions. A man may have quite extensive gummatous disease of the liver without pain or without great enlargement. On the other hand, there can be no question that the most extensive tertiary lesions may be present with a normal or with a very slight elevation of temperature. Among diseases for which the fever is apt to be mistaken are:

Rheumatic Fever.—Nodes growing close to joints may cause peri-articular enlargement with pain, and if fever be present the case may be regarded as one of acute rheumatic fever.

Malaria.—It seems scarcely possible that the two diseases should be mistaken, and yet in the case reported by Sydney Philips there were ague-like chills and the temperature curve was most suggestive. In one of our cases, reported by Fitcher, a physician, aged fifty-nine years, had chills and fever which he himself regarded as malarial (though quinine had had no effect on the condition). When stripped, the diagnosis was easy, as the patient had a rupia-like eruption and tender nodes on the shoulders and sternum.

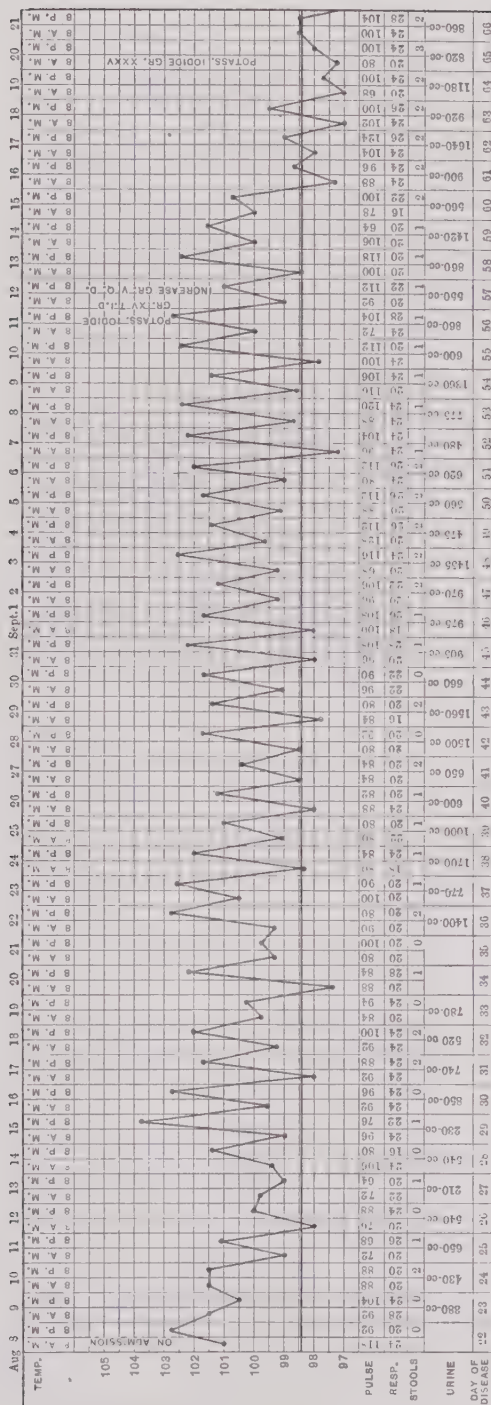
Typhoid Fever.—Cases have been reported in which the syphilitic fever has been mistaken for typhoid. They are rare, however, as J. D. Rolleston states that out of a total of 3076 cases admitted to the London Fever Hospitals wrongly certified to be typhoid fever, only 10 were subsequently found to have syphilis. For weeks the following case, reported in Fitcher's paper, was suspected to be typhoid fever: The patient, aged thirty-nine years, had had irregular fever for three weeks previous to admission. The temperature chart here annexed (Fig. 8) shows an intermittent and remittent fever from August 8 until September 16. There were no malarial parasites. The spleen was enlarged. A continuous fever of this character in the autumn which resisted quinine was naturally regarded as typhoid. It was not until September 12 that suspicion was aroused and W. S. Thayer noted the presence of thickening of the clavicles from old nodes. There was a definite scar on the glans and the patient acknowledged infection. Potassium iodide was given and by September 16 the temperature was normal.

Tuberculosis.—Perhaps more important than any of these is the simulation of pulmonary tuberculosis by syphilitic fever. Many writers have called attention to these cases, and E. G. Janeway brought a series before the Association of American Physicians in 1898. The question of the relation of the two diseases has been considered in a monograph by Sergeant.¹ It is more particularly in the form in which there are sweats, irregular hectic fever, and loss of weight, associated with a slight cough, that tuberculosis is suspected. The absence of well-marked physical signs and of bacilli in the sputum may suffice to call attention to the anomalous nature of a case. The liver is very often enlarged, irregular, and tender, and it is this feature that may suggest the proper treatment, which is, as a rule, followed by prompt recovery.

It is by no means easy to see why fever is present in some cases of syphilis and absent in others. In many instances the liver is involved,

¹ *Syphilis et tuberculose*, Paris, 1907.

Fig. 8



Fever curve suggesting typhoid fever.

and it has been suggested that the damage to this organ is sufficient to prevent its proper action as a filter, and in consequence fever-producing substances reach the general circulation. In a few cases gummata become secondarily infected by pyogenic organisms, but this is exceedingly rare.

2. *Specific Symptoms of Secondary Syphilis.*—*Syphilitic arthritis* is very frequently complained of. It usually takes the form of dull pains in the joints of the extremities—much like the “growing pains” of children, or of “rheumatism,” and is frequently regarded by the laity as rheumatic in character. The joints are usually not swollen, tender or red, although a small effusion may be present. The pains are, as a rule, not severe, but are worse at night and may be intense. They persist for a longer or shorter period, then disappear without apparent cause, and often return at irregular intervals. They resist all measures except specific treatment. More characteristic still are the pains in the periosteum of the long bones; the clavicle, sternum, tibia, and humerus are most frequently affected. When the bones of the head are involved, dull, remittent headaches occur. These pains are usually worse at night and are out of all proportion to objective signs; the latter are, as a rule, absent, although there may be swelling of the periosteum and even a definite periostitis. The muscles and joints are often stiff and sore.

Ocular symptoms are often present. The most frequent of these is iritis. At first only one eye but finally both are involved. The iritis may be plastic, serous, or gummatous. The third form alone is peculiar to lues. It is accompanied by all the signs and symptoms of ordinary iritis. In addition one or more yellowish or yellowish-red, nodular elevations are seen, varying in size from a hemp-seed to a small pea. They are situated in the pupillary margin, on the ciliary border or between the two, but they tend to coalesce. The prognosis is doubtful on account of the frequent formation of posterior synechiæ.

Disturbances of the nervous system are frequent and of the gravest import. They are sometimes responsible for death during the secondary stage. Their full treatment belongs to neurology and they will be dealt with subsequently. The most serious involvements are due to the characteristic acute arteritis, thrombosis of the cerebral arteries with softening being a not infrequent occurrence. Actual rupture of a syphilitic artery (the frequent cause of apoplexy in the young) is usually a phenomenon of the tertiary stage, and is due to a gummatous change in the vessel wall. Acute meningomyelitis, peripheral neuritides, and compression paralysis due to periosteal lesions are fairly common.

Functional disturbances are not uncommon. Fenger and others have shown that the skin and tendon reflexes are first increased and then depressed, sometimes finally disappearing.

Visceral lesions are so much more characteristic of tertiary lues than of secondary that they are described together. There are, however, sundry symptoms occurring in the secondary stage, which are undoubtedly due to some pathological change in the viscera and which may run imperceptibly into the tertiary symptoms which arise from gummatous inflammations. The bone symptoms are an example. In addition to

the "rheumatic" pains already described, a periostitis with the appearance of painful and tender nodules is not uncommon; and an osteitis with the formation of exostoses is occasionally seen, particularly in the tibia. So, too, there may be arthritis with effusion, which may even be polyarticular and resemble rheumatic fever. Serous exudation is also seen occasionally in the tendons and bursæ. The involvement of the liver in some pathological change is probably to be inferred from the jaundice which sometimes appears early.

Cutaneous and mucous lesions are the most characteristic and constant manifestations of secondary syphilis. Nowhere is the wanton nature of the disease more obvious than in its skin lesions; for there is hardly a single cutaneous affection which lues may not simulate. The cutaneous syphilides, however, have certain common characteristics which distinguish them in part or in whole from other skin diseases. These are as follows:

- (a) The syphilitic lesions are usually circular or approximately so.
- (b) Their evolution is slow and the successive crops of eruption are dissimilar.
- (c) They are more or less symmetrical in their distribution, showing a tendency to grouping, particularly in circles and semicircles.
- (d) They have a characteristic reddish-copper color, which resembles raw ham.
- (e) They are usually indurated and often present at the periphery a raised collarette (the *collerette* of Bielt).
- (f) They usually cause no itching or other subjective symptoms, although in occasional cases pain is marked.
- (g) They tend to resolve, although often leaving behind them scars, not infrequently pigmented. (In the precocious, malignant syphilide rapid ulceration with extensive tissue destruction occurs.)
- (h) They tend to become generalized and to involve large areas of skin. When localized, they have certain seats of predilection—the forehead (*corona veneris*), the extremities, the anogenital region, etc. The dorsal surfaces of the hands, wrists, and feet are exempt, and the sternal and clavicular regions are rarely involved except in the late destructive lesions.
- (i) The scales are thinner, more superficial and less abundant than those seen in non-luetic lesions; they are dirty gray and do not glisten.
- (j) The crusts are gray, greenish brown, or black; they are made up of superimposed layers; the surfaces are rough and laminated, and they are more easily detached and thicker than in non-syphilitic lesions.
- (k) The ulcerations tend to be kidney- or horseshoe-shaped.
- (l) The lesions are altered by climate, age, sex, alcoholism, and the presence of so-called "diatheses." This is particularly marked in seborrhœic individuals, in whom the luetic eruptions often take on seborrhœic characteristics (the "interlocking of seborrhœa and lues" of Unna). This characteristic is known as syphilitic imitation.
- (m) Finally, they are polymorphous, often manifesting themselves simultaneously in various forms,

The most frequent lesions are:

1. *Syphilitic Roseola*.—The secondary stage is oftenest inaugurated by the appearance of a measly, rosculous rash, and this event may be said to end the second incubation period. It takes place about the forty-fifth day after the appearance of the chancre. The rash usually appears first on the flanks and the sides of the thorax; thence it extends to the trunk and the extensor surfaces of the limbs. The face and hands are, as a rule, not involved. The rash consists of small, flat, usually round or oval macular spots. They are all of about the same size and are widely disseminated. At first they are rose-colored, later becoming darker, wine-colored, and finally fading into a pinkish yellow. Pressure makes them disappear only in the early stages. If observed through blue glass, as advised by Broca, the macules always become more apparent, and they may be recognized in this way when not otherwise visible. Occasionally the lesions are somewhat raised, like the wheals of urticaria. The rash comes out slowly; it then persists for several weeks and finally gradually disappears. In some cases its whole course is a rapid one. Recurrences are not infrequent, and luetic patients may exhibit repeated macular eruptions at intervals even of years.

The diagnosis of syphilitic roseola from other macular cutaneous affections sometime presents a good deal of difficulty. Measles and pityriasis rosea are the two diseases most frequently to be differentiated. As a rule, the history, the nature of the accompanying constitutional and other disturbances, and careful examination of the lesions for specific luetic characteristics will make the diagnosis. The frequent involvement of the face in the rash of measles and its rare involvement in syphilis is an important point in the differential diagnosis. Other acute exanthemata, medicinal rashes, the eruptions of typhus and typhoid, erythema, and the roseola of gonorrhœa may also be mistaken for the macular syphilide.

2. *The Papular Eruption*.—This represents the second state in the evolution of the cutaneous syphilide. It usually follows the roseola by a short interval, but in some instances it comes out before the latter has disappeared; and its appearance may, on the other hand, be much delayed. The eruption consists of round, or nearly round, reddish, raised papules, varying in size from a lentil to a ten-cent piece. The lesions may be quite intact, but are often covered with a slightly squamous epidermis. They are situated most often on the trunk and face. Not infrequently they lie arranged in groups around a central element (syphilide papuleuse en corymbes of the French). The miliary or lichenoid form of papule deserves special description. When appearing early the lesions are very numerous and usually uniformly distributed; the abdomen, back, limbs, and face may be covered.

In its late form, the papular syphilide appears generally three or four months after the onset of the disease and the lesions are much less numerous. It is a polymorphous eruption, but the lesions are in general miliary and of a reddish-brown color. They are not infrequently capped by a small pustule, or covered with a crust or a scale. They are arranged in groups, often like constellations. Another more special form of papular syphilide often seen and of great interest from a diagnostic stand-

point is the badly named syphilitic psoriasis. Here the lesion is a large copper- or ham-colored one, occupying a large extent of body surface (face or limbs). The edges are often indistinct, and the lesion consists of numerous concentric circles. On the surface the epidermis is partly detached in the form of dirty, dry scales, which may be easily removed without bleeding. Fissures and rhagades often accompany this syphilide, and its resemblance to ordinary psoriasis is obvious; but the localization, the rapid evolution, the influence of specific treatment and the appearance of the scales, together with the general clinical features of the case, are usually sufficient to make the diagnosis.

The large papular or lenticular syphilide is quite commonly seen. It shows a predilection for sites about the natural orifices of the body; but is also seen on the neck, trunk, chin, and palms. It may appear at any time in the secondary stage and be the only cutaneous manifestation. Often it occurs simultaneously with the mucous patches. The lenticular papule is the most common and characteristic of the papular eruptions. The lesions are round or oval, with sharp borders and slight elevation. At first they are small and red, but later become copper-colored. The surface becomes shiny, the lesion breaks at its centre and desquamates. The desquamation is repeated until finally the lesions disappear, leaving behind them brownish or bluish-gray spots. The eruption usually starts on the forehead (*corona veneris*) or the nape of the neck; it then spreads to the abdomen and in two weeks is pretty well generalized. It comes out in crops and may last for ten months.

The papular rash sometimes becomes *nummular*. Here the lesions are large, with marked umbilication and a tendency to desquamation. Later they become annular, with a ring-shaped periphery of induration persisting. Intersection and interfusion of such circular, semicircular, and elliptical patches give a dreadful and bizarre appearance.

The secondary papular syphiloderm of the palms and soles (*psoriasis palmaris et plantaris syphilitica*) appears as lentil-sized, non-elevated, brownish spots, which are indurated and evolve slowly. When retrogressive changes begin, a white, glistening scale forms at the centre, surmounting a smooth, reddish depression. A collar of semidetached scales forms around the papule and a brown stain is left after the disappearance of the lesion. Fissures and ulcerations are not uncommon. The syphilide is chronic in its course, obstinate to treatment, and frequently relapses. It is pathognomonic of lues, but must be distinguished from eczema and, rarely, from psoriasis.

The moist papule or broad condyloma occurs where the lesion is exposed to warmth or maceration. Neglect and uncleanness favor its development. It appears as a flat, button-like excrescence, often much elevated above the surrounding skin; its surface may be papillary, is denuded of epithelium, and covered by a layer of dirty, grayish material, which is usually bathed in a foul, thin secretion. Condylomata are much commoner in women than in men. The lesions are most often bilateral and are extremely infectious. They hypertrophy, particularly when neglected, and may then coalesce, forming extensive, flattened, mushroom excrescences. Condylomata occur most often about the

anus; but they are also frequently seen on the vulva, perineum, scrotum, thigh, etc. They are very liable to recur frequently. The diagnosis is, as a rule, easy.

3. *The Vesicular Syphilide*.—This form is excessively rare and is ephemeral when it occurs at all, being soon replaced by crusts. Small vesicles are sometimes seen in connection with the miliary papule. It is doubtful if true bullæ ever occur.

4. *The pustular syphilide* is, on the whole, rare in the secondary stage, and its occurrence then usually indicates a severe type of the disease. It occurs most often in cachectic or debilitated subjects. It is the latest of the secondary eruptions, is obstinate to treatment and prone to relapse. The pustules vary in size from small, acuminate, acne-like lesions to large, pustulocrustaceous forms. Syphilitic polymorphism is well exhibited by the pustular syphilide, the lesions varying in size, number, distribution, and extent of suppuration. The lesion may resemble any of the pustular skin diseases (acne, ecthyma, varicella, impetigo, etc.); but two clinical forms, the small and the large pustular syphiloderm, should be recognized.

The small pustular syphiloderm resembles acne in many respects. The lesions, which develop from papules, are small, grow slowly, and often remain stationary for weeks, drying up finally into yellow crusts. In the early form the pustules are very numerous and are well scattered over the body. In the later forms they tend to be grouped on the scalp, elbows, knees, etc. Successive crops of small pustules often follow one another for months. In the diagnosis the distinction from acne, variola, and varicella offers the chief difficulty.

The large pustular syphiloderm begins as the large lenticular papule, which rapidly becomes pustular; the pustule soon ruptures or dries up into a crust, removal of which shows an ulceration beneath. When the ulceration heals a brown, pigmented scar is left behind. The lesion, however, usually lasts for a long while, the crusts heaping up to form the *rupia syphilitica*. This rupial eruption is frequent and striking. It begins as a flat papule, which becomes bullous or purulent, and is surrounded by a livid inflammatory areola. The pustule ruptures and the contents dry into brown or black crusts under which ulceration continues. The crusts, in this way, become stratified and thickened (oyster-shell appearance). The base increases in size and the lesion in height, becoming finally cone-shaped. If the crusts are removed an indolent ulcer is exposed with abrupt, undermined edges, and containing serosanguineous pus. The diagnosis between the large pustular syphiloderm and variola is sometimes very difficult. The syphiloderm, however, makes its appearance more slowly, begins upon the trunk and not upon the face, and shows the concomitant signs of lues.

It is not certain whether the pustular syphilide is the result of an actual secondary invasion or not. Unna has shown that such an invasion is very rarely demonstrable.

5. *The tuberculous and ulcerated syphilide* merges into the papular syphiloderm on the one hand and the gumma on the other. It does not usually appear until about two years after the initial sore. When occur-

ring early it signifies a grave form of the disease. The lesions are circumscribed, brownish-red, bean- to walnut-sized infiltrated tumors, usually relatively few in number and tending to be grouped, particularly upon the nose and forehead. The course is chronic, the lesions disappearing either by absorption or ulceration. When the lesions are few and situated on the face the similarity with lupus vulgaris may be very striking.

The ulcerated syphilide is either the subsequent stage of the tuberculous syphilide or appears as a manifestation of the rapid malignant form of syphilis. The lesions appear as red, brownish tubercles, which soon soften and ulcerate. There is an irregular loss of substance, with suppuration. This may be extensive, causing great deformity. If the lesion heals, it persists for a while as a reddish infiltration, with a protruding border and covered by a crust. It may be 3 or 4 cm. in diameter. When it disappears it leaves behind it a marked scar, often with a surrounding area of pigment. The lesion may be situated anywhere on the body, but is most often on the legs. It occurs most frequently in weak subjects and may follow the chancre immediately.

6. *Pigmented Syphilide*.—This cutaneous lesion appears six to twenty-six months after the chancre; it is unique among the cutaneous syphilides in its resistance to specific treatment; it is accompanied by no symptoms and is sometimes regarded as a parasymphilitic manifestation. It is most frequent in young patients and is oftener seen in women than in men. It is called by German writers syphilitic leukoderma and consists of large, non-elevated, confluent, grayish patches enclosing circular or oval areas of normal skin among them. The general arrangement suggests lace with large meshes. The non-colored portions of skin appear, by contrast, whiter than normal skin. The rash is almost always situated on the sides of the neck and is symmetrically disposed; it is also seen in front of the axillæ, on the sides of the abdomen, and on the flanks. Occasionally it occurs on the entire body. It often occurs without having been preceded by any other eruption. Its pathology is not clear; Unna and the French consider the pigmented syphilide as a primary cutaneous manifestation of the disease; the Germans regard it as the remains of an old eruption.

7. *Changes in the Hair and Nails*.—Alopecia is a frequent and well-known, although by no means constant, sign of secondary syphilis. It appears during the third or fourth month of the disease, and may be either general or circumscribed (alopecia alveolaris). At first single hairs fall out; later spots of alopecia, varying in size from a lentil to a silver dollar, gradually appear. There are no broken hairs in the spots—an important fact for diagnosis. The alopecia often occurs simultaneously with the pigmented syphilide of the neck. The eyebrows at the same time may be affected and sometimes fall out entirely. The hair is reproduced after syphilitic alopecia and the prognosis is, therefore, almost invariably good. The fall of the hair is due to a folliculitis of the hair follicles; it is accompanied by decoloration of the deep portions of the hair and by a dilatation of the small vessels about the follicle. Changes in the nails are not infrequent. The nails may be cracked or hypertrophied; and often there is an accompanying involvement of the periungual tissues (syphilitic onychia and paronychia).

8. *Lesions of the Mucous Membranes.*—These are among the most important and constant manifestations. On account of their extreme virulence they are a grave feature as regards the spread of the disease. All the lesions seen on the skin may also occur on the mucous membranes; but the most characteristic lesion is the well-known mucous patch. This is seen oftenest in the mouth and consists of a reddish or characteristically opal, slightly raised, papular area, topped by a small erosion. It occurs at various places in the buccal cavity, quite often on the tonsils; and is seen oftenest in mouths subject to some irritation like that of tobacco. When the mucous patch occurs on a site subject to mechanical irritation and to neglect (on the vulva, about the anus, etc.) its character changes and it is called a condyloma. It becomes larger, protrudes, is covered by fungous, papillomatous growths, and has an abundant, foul secretion. This may ulcerate and become diphtheroid. Mucous patches often recur many times.

The mucous patches may become confluent and cover large areas. Rhagades and painful fissures are often associated with them. They may cause marked subjective symptoms. Mucous patches are to be diagnosed from mercurial stomatitis, leukoplakia buccalis, and aphthous erosions. Their frequent occurrence on the tonsils and soft palate is an important point in diagnosis.

The macular, papular, and even pustular syphilides may be situated in the mouth. The angina syphilitica, of greatest interest on account of its clinical importance as one of the early signs of constitutional syphilis, is the most frequent of these buccal syphilides. It consists in a reddening of the tonsils, the pharynx, the uvula, or the soft palate, which is sharply defined anteriorly. It gives the patient little trouble as a rule. Syphilitic laryngitis is also not infrequently seen. In these cases the voice acquires a peculiar roughness which may progress even to complete aphonia.

Late Secondary Syphilis.—This is a form of the disease to which Fournier has given special attention.¹ It consists of secondary phenomena manifested late in the disease, and of such cases Fournier found nearly 1100 examples in a series of 19,000 syphilitic patients. The symptoms may occur at any period of the disease, even so late as in the thirty-first year. What is most interesting is that the late secondary phenomena apparently occur most often in the cases which have been well treated, in direct contradistinction to the tertiary phenomena. This does not contra-indicate efficient treatment, for it is the tertiary phenomena which are to be feared. Any of the secondary symptoms may occur in this form of the disease, but the following are most often seen:

(a) *Cutaneous Syphilides.*—Any one of the secondary eruptions may occur, but when seen in this late stage the peculiar feature of them is their attenuated, abortive character. The recurrent roseola, for example, consists of circumscribed, regional, discrete, large, pale, and tender lesions. Quite frequent, too, is the tertiary erythema, which consists of a single, very superficial reddening of the skin, without infiltration, and free from scales.

¹ *Syphilis secondaire tardive*, A. Fournier, Paris, 1906.

(b) *Iritis*, which is essentially a secondary phenomenon, may occur in the tertiary stage and even years after the chancre.

(c) Most important are the *mucous syphilides*, particularly those of the mouth, which, in the secondary form, occur with extraordinary frequency long after the secondary stage. *Glossite dépapillante* and many scrotal and genital syphilides are among the most common secondary mucous lesions seen in the late stage.

These are not in themselves serious but are particularly important from the standpoint of contagion. "Late secondary syphilis has for a corollary late syphilitic contagion." In view of these facts one should watch carefully the cases of benign recurring syphilis (with recrudescences of secondary manifestations), and particularly the cases complicated by nicotine stomatitis, which seems to be a determining factor in the occurrence of the glossitis so characteristic of late secondary syphilis.

The Tertiary Stage.—The secondary stage has no sharply marked terminal limit; but as it progresses the intervals of freedom from symptoms increase in extent and the symptoms themselves diminished in severity until finally an extended period of latency supervenes. This may, indeed, continue throughout the patient's life and mark the end of the disease; on the other hand, it may mean only an abatement of symptoms which, with the advent of the tertiary stage, again appear. On the average the tertiary phenomena appear about three or four years after the chancre; but they may, in precocious cases of galloping syphilis, be present at the end of a few months, and in others they succeed the secondary phenomena without any interval of freedom from symptoms. They may again appear as late as fifty-five years after the initial sclerosis, and in a fair proportion of cases they are wanting altogether. They may be preceded by any one of a group of Hutchinson's so-called "intermediate symptoms:" gumma of the testicle, psoriasis palmaris, choroiditis, arterial disease expressed in convulsions, visceral engorgement, nervous symptoms (retinitis, etc.), and rupia.

Just what determines the appearance of tertiary symptoms is not known. Certainly the absence of treatment, as Fournier so strongly insists, is an important factor; out of 2396 cases of tertiarism collected by him, 78 per cent. had not been treated at all, 19 per cent. had received moderate treatment, and only 3 per cent. had been properly treated. On the other hand, the gravity of the early syphilis bears no distinct relation to the probability of the appearance of tertiary symptoms; benign cases, and even cases without secondary symptoms, often pass through a typical and even a severe tertiary stage. Alcoholism and all conditions favoring lowered resistance seem to predispose to tertiary syphilis. In general the lesions of the tertiary stage are distinguished from those of the secondary by their lack of orderly appearance and progression, by their persistence, by their asymmetrical and local arrangement, by their relative non-infectiousness, and by their tendency to ulceration.

The Visceral Affections.—These form a most important clinical group. They are not, it is true, absolutely confined to the tertiary stage, but as

they are much more frequent than at earlier stages, it is convenient to consider them together in this place.

I. Syphilis of the Respiratory System.—1. **TRACHEA AND BRONCHI.**—Tracheal and bronchial catarrh may occur in the secondary stage. Later there are more serious lesions, which while relatively rare have great importance from the fact that in almost every instance life is threatened, and the mortality in the whole group of cases is very high. L. A. Connor has studied the subject very thoroughly.¹ In an analysis of 128 recorded cases men and women were about equally affected. In 10 cases the lesions were ascribed to congenital syphilis. The average duration of the infection was about ten years; 97 of the cases came to autopsy. The lesions were: (a) *Gummata*, 20 cases; the lesions were sometimes single, in others the tumor extended over a considerable area of the trachea or involved the whole circumference; (b) *ulcers* were present in 44 per cent. of the cases, and, as a rule, were large and deep. In many cases the cartilages were eroded and fragments had been coughed up. Perforation of the trachea or of a bronchus occurred in 12 cases, in 5 with fatal hemorrhage. This group is very important with reference to the acute ulcerative perforation of large bloodvessels. In 2 cases an ulcer of the right bronchus perforated a branch of the pulmonary artery. In the case of Bernays, of St. Louis, a small ulcer of the trachea perforated the arch of the aorta. In Turner's case an ulcer just above the orifice of the right bronchus perforated the superior vena cava, and in Watson's case an ulcer of the left bronchus perforated a branch of the bronchial artery. In 2 instances the œsophagus was perforated. In several cases the ulcer perforated into the peritracheal tissues, with the formation of an abscess and once with tracheocele; (c) *endotracheal scarring and contractions*; in 40 per cent. of the cases there were scars, bands, or obliterative endotracheitis, with marked stenosis. In some of these cases ulceration seems not to have been a preceding condition, but a slow, progressive proliferation of the submucous tissues has led to gradual narrowing of the lumen; (d) *fibrous peritracheitis*; of this there were 8 cases in Connor's series. The trachea and the main bronchi are encased in a dense mass of connective tissue which had involved not infrequently the recurrent laryngeal nerves. It is probable that the peritracheal lesions in syphilis start as gummata of the lymph glands between the trachea and the œsophagus, and finally lead to a fibrous peritracheitis.

The associated lesions are most important. Syphilis of the lungs was present in 10 cases. Dilatation of the trachea was present 3 times, in each instance above the point of stricture. It is remarkable that bronchiectasis was not more frequent, only 20 per cent., considering that in all but about 15 per cent. of the cases obstruction of some sort existed.

Symptoms.—Cough, dyspnoea (often paroxysmal), and stridor are the special features. The expectoration is often blood-stained, purulent, and fetid, sometimes containing fragments of tracheal cartilages. Profuse hemorrhage, when it occurs, is usually from a large vessel and is promptly

¹ *Amer. Jour. Med. Sci.*, 1903, cxxvi, 57.

fatal. Progressive dyspnoea, one of the most constant symptoms, is usually associated with attacks of orthopnoea and cyanosis, which may come on with great suddenness and rapidly prove fatal. This peculiar feature of paroxysmal, intermittent dyspnoea has attracted the attention of many writers. Grossmann and others regard this type of dyspnoea as an effect rather of cardiac insufficiency than of the actual stenosis. No symptom is more striking than the stridor, which is present in about 50 per cent. of the cases. It may occur with inspiration alone or with both acts. It may be of the loud, roaring character; more commonly it is of higher pitch and sometimes it is quite sibilant. Among other symptoms are pain, which is not very frequent, and tenderness over the trachea. Aphonia was present in some cases even when the larynx was normal. Retraction of tissues at the root of the neck during inspiration is not infrequent. Gerhardt called attention to the limitation of the vertical movement of the larynx in tracheal stenosis as an important differential sign from the laryngeal form.

The *diagnosis* is not often made in the cases without stenosis, unless ulcers and scars are seen in the trachea by laryngoscopical examination. With tracheal or bronchial narrowing the clinical picture is very definite: (1) A peculiar type of dyspnoeic breathing in which the prolonged, labored, and relatively slight inspiration and the shorter, easy expiration follow each other without the usual pauses; (2) a stridulous sound, chiefly or altogether inspiratory; (3) in most cases an inspiratory sinking in of the tissues of the root of the neck, the epigastrium, and the lower intercostal spaces. (Connor.)

The *prognosis* is grave; the mortality among 128 cases was 76 per cent. In 11 of the cases death occurred in an attack of suffocative dyspnoea, in 4 it was due to hemorrhage. The *treatment* is not very satisfactory. In a few cases antisypilitic measures have been successful. Schroetter has treated some cases successfully with dilatation, which has been practised even in narrowing of a main bronchus. Tracheotomy was performed in 17 cases of Connor's list, in only 2 with permanent improvement.

2. LUNG.—With the discovery of the specific organism we may expect more light on the problem of pulmonary syphilis. All are agreed that the lungs are rarely attacked, few are agreed as to the distinctive features of the lesions, and fewer still as to the clinical symptoms.

Many of the old writers in the sixteenth and seventeenth centuries spoke of a phthisis originating in lues, but it was not until the latter half of the nineteenth century that the attention of pathologists was particularly directed to the subject. Depaul in France, Virchow and Wagner in Germany, were the first to describe the lesions in the congenital and acquired forms. The literature is very fully given by Flockermann¹ and Herxheimer.² Anatomically the disease is rare. Among 2500 autopsies at the Johns Hopkins Hospital there were 12 cases in which lesions believed to be syphilitic were present. J. K. Fowler, who has given us

¹ *Centralblatt f. allg. Path.*, Band x.

² Lubarsch und Ostertag, *Ergebnisse*, Jahrg. xi, 1907.

the best study of the disease which has appeared in English,¹ was only able to find 12 specimens in the London museums, and 2 of these were of a doubtful nature.

Clinically the disease is rarely recognized. In not one of the cases seen by the senior writer in which the condition was suspected was it certain, and in none of these was the diagnosis confirmed postmortem. On the other hand, there are clinicians who believe that a great many cases which we regard as tuberculous have in reality a syphilitic origin. The difficulty in reaching the conclusions as to the nature of a case may be gathered from the fact that of Hiller's 84 collected cases with autopsies, Councilman regards only 28 as shown to be definitely syphilitic. It is more convenient to consider the congenital and acquired conditions separately.

Congenital Pulmonary Syphilis.-Gummata are exceedingly rare. The common lesion is the so-called *white pneumonia*. Virchow described in the lungs of stillborn children a diffuse change, sometimes involving all the lobes and causing a marked consolidation with great increase in volume. While the children, as a rule, are stillborn and premature, yet sometimes they are born at term and live for several hours. In other cases or in other parts of the same lung the surface is less uniform, and presents a more grayish tint, and is firmer, indicating that sclerotic changes have occurred. This so-called interstitial pneumonia is only an advanced stage of the other process and is due to the great increase in the alveolar and interlobular connective tissue. Sections prepared by proper methods show in these lesions an extraordinary number of spirochetes. While the majority of all cases of congenital pulmonary syphilis have only an anatomical interest, there are a few cases in which the lesions have appeared later in life; but it may be very difficult to determine the exact nature, as the coexistence of tuberculosis with syphilis in young infants is not uncommon.

(1) *Acquired Syphilis.*-The lesions may be described as follows: *Gummata* are rare and involve, as a rule, the neighborhood of the hilus and the lower lobes. They have the usual appearances of these structures and vary in size from a hazelnut to a hen's egg. They may soften and break into bronchi, or they may undergo sclerotic changes leading to extensive shrinkage of the lung tissue and to bronchiectasis. (2) *Bronchopneumonia*. Orth and others regard an exudative syphilitic pneumonia as very doubtful. New investigations should now determine this point. The case recorded by Délépine and Sisley² shows one way in which the lung may be involved. An enormous gumma of the right lobe of the liver, measuring five and one-half by four and one-half inches in extent, pushed up the diaphragm, to which it was firmly adherent, and extended through and involved the lower lobe of the lung. There were patches of caseous pneumonia and others looking like catarrhal pneumonia. With these there was sclerotic induration. The specimen, one of the most remarkable ever described, is well figured in Rolleston's work on the liver.

¹ *Diseases of the Lungs*, London, 1898.

² *Pathological Society Transactions*, London, xlii.

(3) *Sclerotic patches, chronic interstitial pneumonia.* At the root of a lung, more particularly, but scattered anywhere throughout the tissues, sometimes mapping out a large group of lobules, or radiating from the hilus of the lung, are long strands of fibrous tissue fissuring and dividing the organ, the *pulmolobatus* of Virchow. In advanced cases bronchiectasis occurs, or there may be cavity formation. When these scars occur alone, without gummata in the neighborhood and without signs of syphilis elsewhere, it is impossible to determine their exact nature. On the other hand, when such lesions coexist with gummata, or when they actually surround or extend from them, the syphilitic character is evident.

The *symptoms* of pulmonary syphilis are very uncertain. Practically they are those of tuberculosis, but with the physical signs more commonly at the root of the lung and toward the base. The clinical features are often those of chronic bronchiectasis or fibroid phthisis. In the cases with tracheal or bronchial stenosis dyspnea is a special feature. Hemoptysis may occur. There may be no fever, but when softening has occurred or when there are large bronchiectatic cavities the temperature may be of the hectic type. J. K. Fowler lays down the following conditions necessary to determine the syphilitic nature of a case with progressive disease of the lung: "(1) The cases must be complete, that is, the symptoms observed during life must be considered in connection with the lesions described in postmortem examination; (2) the evidence of syphilitic infection must be undoubted; (3) repeated examination of the sputum must have been made and tubercle bacilli have been invariably absent, and the absence of tubercle from the lungs (as the cause of the lesions) must be proved by postmortem examination; (4) syphilitic lesions about the nature of which there can be no doubt must be found in other organs."

The *relations of syphilis and tuberculosis* are thus described by the same writer with admirable clearness. "(1) Tubercle usually affects the apex of the lung and subsequently the apex of the lower lobe and tends to progress in a certain route. The primary lesion of syphilis is often about the root and central part of the lung. The disease follows no definite line of march and gummata may be found in any position. (2) Both tuberculosis and gumma may undergo either necrosis and caseation or fibrous transformation, but with caseous tubercle the tendency toward softening and cavity formation is the rule, whereas a caseous gumma very rarely breaks down. (3) The progressive destruction of the lung by a process of disintegration leading to a gradual increase in size of a cavity, a change so commonly observed in tuberculous disease, is rarely if ever observed in syphilis, except as a secondary result of stenosis of one of the main bronchi. (4) In nearly all cases of advanced destruction of the lung occurring in the subjects of syphilis, stenosis either of the trachea or of one of the main bronchi is present, whereas this lesion is very rare indeed in tuberculosis. (5) The cavities found in cases of pulmonary syphilis are usually bronchiectatic, but not invariably so; whereas in tuberculosis they are commonly due to progressive destruction of the lung, but may be bronchiectatic. (6) The tendency

to the formation of pulmonary aneurism, which is so marked a feature in tuberculosis, is rarely observed in pulmonary syphilis. (7) Pulmonary lesions in tuberculosis are very common, whereas in syphilis they are extremely rare." (Fowler.)

11. **Syphilis of the Alimentary Canal and Abdominal Organs.**—1. **SALIVARY GLANDS AND PANCREAS.**—Swelling of the salivary glands occurs in the secondary stage and it may be well-developed before mercurials have been given. The condition may resemble mumps. Chronic bilateral parotitis with enlargement, a not very uncommon condition, is probably not connected with syphilis. Gummata of the salivary glands have been described, sometimes with ulceration.

The *pancreas* is rarely attacked and Herxheimer gives only three cases from the literature, all with gummata.

2. **ESOPHAGUS.**—In a few rare instances ulceration of this part has been seen, usually as an extension from the pharynx. Stenosis as a sequel of the ulceration has been described by Virchow and others.

3. **STOMACH.**—Great difference of opinion exists as to the frequency of syphilitic lesions of this organ. The clinical evidence is by no means trustworthy, as there are men who see a specific gastritis in every disturbance of digestion in a syphilitic patient. The best evidence of its rarity is the fact that in Chiari's 243 postmortems upon syphilitic patients there were only 2 with definite stomach lesions due to the disease.

There are three types of lesions: (a) *Diffuse syphilitic gastritis*, which was present in a syphilitic negro (examined by Flexner) who had gummata on the frontal bone, in the liver, and in one testis.

(b) *Syphilitic Ulcer.*—The majority of clinical cases reported have presented the symptoms of ulcer in connection with the history of syphilis. Fenwick very correctly concludes that in fully one-half of the cases in which the two diseases coexist in the same patient there is no direct relationship between them. The chief evidence of the specific character of the lesions is the ready response to antisyphilitic treatment, perhaps after prolonged trial of other measures. As there seem to be no distinctive features of the syphilitic ulcer, this point has been especially insisted upon, particularly by Stockton and by Einhorn, who have reported interesting cases. Fenwick concludes that "these cases chiefly differ from the simple variety of the disease in three particulars, the first of which is the extreme severity of the pain and vomiting, the second the infrequency of hemorrhage, and the third their obstinacy to ordinary treatment and their great tendency to relapse." We do not, however, think it possible to draw a clear distinction between simple and syphilitic ulcer, although it is well to bear in mind the undoubted existence and the possible frequency of the latter condition.

(c) *Gumma* of the stomach is exceedingly rare. Of the 14 cases collected by Flexner 5 or 6 had positive nodular gummata, the largest formed a flat tumor 8 cm. in extent, with slight ulceration on the surface. In no instance has the diagnosis of a gumma during life been confirmed at autopsy.

In connection with syphilis of the stomach there are two conditions in which tumor may be present. At the pylorus, or in its neighborhood,

there may be nodular thickening, and it is quite possible that in certain of the cases in which gastric tumors have disappeared entirely, the lesion has been specific. Several of the suggestive cases recorded by Einhorn are of this nature. Following the scar of the syphilitic ulcer near the pylorus, the orifice may be narrowed, with the result of great dilatation of the stomach. In a more important group of cases the tumor believed to be in the stomach, is in reality a gumma of the left lobe of the liver. We have seen two or three patients with suspected carcinoma of the stomach with epigastric tumor, in whom the condition has apparently been caused by a gumma on the left lobe of the liver, simulating carcinoma.

4. INTESTINE.—In the small bowel, which is less frequently involved, there may be enteritis, gummata, ulceration with consecutive cicatrization and narrowing. The so-called syphilitic *enteritis* offers nothing peculiar. There is swelling of the lymphatic follicles, sometimes with small ulcers. In long-standing cases of tertiary syphilis with chronic diarrhœa, amyloid degeneration of the mucous membrane is not uncommon, sometimes with ulceration.

Ulcers.—Apart from the follicular ulcers, there may be extensive loss of substance due to the breaking down of gummata. The ulcers involve the lower part of the jejunum and the ileum. In a few cases perforation has taken place. Healing of the ulcers may lead to cicatricial contraction with stenosis, and there are cases on record in which in several places the calibre of the jejunum and ileum was narrowed. Appendicitis has been attributed to syphilis, but there is no evidence that persons with this disease are more frequently attacked than others.

5. RECTUM.—The special liability of this part to the disease is doubtless the result of a direct infection by the secretion, either from the vulva or from condylomata. In a few instances the ulceration follows the breaking down of gummata. The loss of substance, often very extensive, is usually circular, and in healing leads to marked stenosis. The condition is very much more frequent in women than in men. The stage of ulceration may be latent, and the patient is not infrequently first seen when narrowing has already taken place. The wall of the bowel is greatly thickened, the muscular coat much hypertrophied, the mucosa roughened, or actually ulcerated, and the lumen narrowed so as to admit the little finger with difficulty. Periproctitis is a common sequence, and in women the pelvic peritoneum may be greatly thickened. The ulcers may perforate with the formation of a pelvic abscess or a rectovaginal fistula. The diagnosis from carcinoma sometimes offers difficulty, and the syphilitic rectum has been excised for cancer. The greater frequency in women, the marked thickening of the walls with narrowing of the lumen, and the absence of definite marginal growths about the ulcers are important points. The presence of other lesions, the fact of recurring miscarriages in a woman or the presence of syphilitic lesions in the husband may help in the diagnosis. A remarkable form of syphilitic tumor of the pelvis has been described in which the connective tissue is chiefly involved, forming a dense mass in which the organs are embedded. Herxheimer cites 4 cases from the literature and reports 1 of

his own. In one instance the pelvis was occupied by a tumor the size of two fists, situated between the bladder and the rectum, and which during life was thought to be cancer. The mucosa of the rectum may be intact.

6. **SPLEEN.**—In the early stages of the disease enlargement may usually be determined, and Moxon has described an acute syphilitic splenitis.

Gummata are common, particularly when the liver is involved. The substance of the organ may be thickly set with growths varying in size from a walnut to a large orange. Wilks¹ description and figures are excellent, and he was one of the first to recognize the true nature of these bodies. They are very rare in the congenital form (Still).

Gummosus Cicatrices.—More frequently the organ is enlarged, the capsule thickened, the surface indented and scarred and fissured, even divided into four or five sections; the liver and spleen may look very much alike. The greatly enlarged and irregular organ may present a remarkable degree of mobility.

Amyloid Spleen.—In long-standing cases, particularly those with disease of the bone and of the rectum, amyloid change is common, either as a diffuse process with enlargement of the organ or limited to the Malpighian bodies, the so-called sago spleen. In certain cases of syphilis with enlargement of the liver and spleen leukemia may be suspected. In a case of congenital syphilis with an extraordinarily fissured liver, the spleen weighed more than 1500 grams. It was the most prominent feature in the distended abdomen. There was great increase of the leukocytes and the case was regarded as one of leukemia until the postmortem showed the existence of congenital syphilis.

7. **LIVER.**—The literature is very fully given by Herxheimer in Lubarsch and Ostertag's *Ergebnisse*, Jahrg. xi. and the whole subject is discussed at length in Rolleston's work on *Diseases of the Liver*.

Incidence.—It is difficult to determine the frequency with which the liver is involved. Once attention has been called to the subject and the special features have been recognized the cases are found to be not uncommon; in the records at the Johns Hopkins Hospital during a period of eighteen years there were 30 cases diagnosed as such, while in the postmortem room among 2500 autopsies there were 40 cases showing gummata or syphilitic cicatrices (20 of each) and 15 additional cases regarded as syphilitic cirrhosis. The incidence in congenital syphilis has been given at from 40 to 70 per cent. of cases of infants born prematurely or dying shortly after birth.

Morbid Anatomy.—The lesions may be described in four groups: (1) *Diffuse interstitial hepatitis*. This is common in the congenital form, in which the liver is usually enlarged, very firm, with a peculiar color, described as grayish yellow or having more the appearance of flint—the *foie silex* (Gubler). The cut surface may be uniform, and frequently miliary gummata are to be seen. The process may be much more advanced in some parts of the liver than in others, and there may be large areas of fibrosis. (2) *Gummata*. These consist of large, opaque,

¹ *Transactions of the Pathological Society of London*, 1871.

white tumors, usually firm and solid, the cut surface resembling a section of potato and much denser and harder than the ordinary cheesy matter of tuberculosis. Surrounding the gumma is a definite zone or capsule of connective tissue, and outside that a zone of translucent tissue representing the small-celled infiltration of the advancing syphilitic process. In fresh gummata of all sizes the three zones may be recognized. In old ones the translucent zone is absent. The tumors vary in size from small nodules of from 2 to 4 mm. in diameter to huge tumors the size of two fists. They may be solitary, more frequently there are from 3 to 4 or in some instances 12 or more. Gummata undergo retrogressive changes. Just as the massive subcutaneous, muscular, or periosteal tumors, those of the liver may disappear completely, leaving only a fibrous scar. Softening may occur in the centre of a large gumma, either from the breaking down of the necrotic tissue or occasionally from septic infection. No change may occur in the consistency of a large gumma while it is undergoing even rapid absorption. Calcification may occur, and the rare instances of diffuse calcification in wide areas in the liver have probably been of this character. (3) *The scarred and the botryoid liver.* There may be (a) small, puckered depressions on the surface, with perihepatitis, but with very little actual deformity of the organ. These small scars may be central as well as peripheral. There may be nothing in the liver itself to show that these are the remains of healed gummata, but specific lesions may be present elsewhere or in the other parts of the organ itself. (b) One or both lobes may be divided by bands of fibrous tissue, radiating irregularly from the hilus or following the portal canals. The bands may be from 5 to 10 mm. or more in diameter and the lobes may be greatly puckered and deformed. Sometimes there are gummata associated with these cicatrices. In extreme cases the whole surface of the organ is lobulated, and to this condition the term "botryoid" has been given. In a still more extreme form large sections of the liver may be completely isolated, or the organ may be made up of three or four sections united by flat bands of connective tissue. The liver substance may look natural or show slight cirrhotic changes. Occasionally it is amyloid. (c) Amyloid change may coexist with gummata, or it may occur independently in long-standing tertiary lesions.

Symptoms.—Congenital.—In the majority of cases the infants do not live. In children under two years the luetic appearance, together with an enlarged abdomen due to an increased size of the liver and the spleen, are the most usual manifestations. The enlargement of the liver is uniform and may be very great, reaching below the level of the navel. Tumors are very rarely felt, but the organ is firm; very often the edge may be pressed readily with the finger, or through a thin-walled abdomen the shadow of the edge of the organ may be seen to descend with inspiration. As Gee pointed out years ago, enlargement of the spleen is almost constant in syphilitic children. Jaundice is not very common and when it occurs is early. Ascites is rare.

In general practice a much more important group of cases is the syphilitic hepatitis which occurs as a late manifestation. The attention of the senior author was called to this form by a very remarkable case

in the practice of Palmer Howard, of Montreal: A boy, aged ten years, had for several months obscure abdominal trouble with enlargement of the liver, slight jaundice, ascites, and enlargement of the spleen. Finally, definite, irregular nodules were felt on the liver, whether tuberculous or malignant we were in doubt. One day his father was discovered to have a very characteristic palmar psoriasis. He confessed to having had a syphilitic infection as a young man. This gave us the diagnosis, and after months of serious illness the boy recovered promptly and is still alive, over thirty years after the attack. Since that date a number of very interesting cases have been seen, several of which have been reported.¹

J. G. Forbes² has analyzed 132 cases of late congenital syphilis and in 34 per cent. the liver was involved, coming next to the bones (39 per cent.) as the seat of disease. The age incidence is worth noting—the first decade 26.5 per cent., second decade 57.5 per cent., third decade 12.3 per cent., fourth decade 3.7 per cent. The clinical features are often very characteristic. The facies, the interstitial keratitis, the rhagades, the Hutchinsonian teeth, the dwarfed stature, sometimes infantilism, or the clubbed fingers—one or other of these points may clinch the diagnosis in an obscure abdominal case with symptoms pointing to the liver. The symptoms do not differ materially from those of adult syphilis of the liver and there may be the three groups of cases: the enlarged, irregular liver, with pain due to the perihepatitis; fever, and an obscure abdominal condition the nature of which is entirely overlooked unless some clue is furnished. The second group of cases, those with tumor on the surface of the right or left lobe, present no special features, and lastly there may be a final stage of the syphilitic hepatitis in which there is portal constriction, enlarged spleen, and ascites. In certain of those cases there may be marked leukocytosis and a clinical picture resembling leukemia.

Clinical Features in the Adult.—The manifestations are most varied and the cases may be grouped, as Rolleston suggests, into (1) those with *features of hypertrophic cirrhosis*. A man with a history of a primary sore has pains in the region of the liver, slight jaundice, and on examination the organ is found to be enlarged, reaching to the navel or even a hand-breadth below it. It is usually tender and possibly a little irregular, but in some cases it may be quite smooth. (2) The cases resembling ordinary *atrophic cirrhosis with recurring ascites*, enlarged spleen, and all the ordinary features of hepatic dropsy. The portal obstruction may be due to direct pressure of large gummata on the main branches, or the stenosis may follow cicatrization. In the *Lectures on Abdominal Tumors* a case of this character is reported: this was a woman who had been very frequently tapped before admission, and in whom the diagnosis of syphilitic hepatitis was made by the accidental examination of her shins. She recovered promptly and some years afterward died suddenly. The liver showed the old healed gummata. Undoubtedly many of the cases of "cured alcoholic cirrhosis" are of this nature. It is sometimes

¹ *Lectures on Abdominal Tumors*, 1895.

² *St. Bartholomew's Hospital Reports*, xxxviii, 37.

impossible to get positive evidence of syphilis, but in a patient who has been going from bad to worse and has had to be tapped repeatedly, if recovery occurs promptly under syphilitic treatment, it is fairly good evidence as to the nature of the disease. (3) *Hepatic Tumors*. The syphiloma on the surface of the right or left lobe may form a visible or palpable tumor, or there may be multiple nodules on the surface of the organ. Several very characteristic cases are reported in the *Lectures on Abdominal Tumors*. There may be a small, solid nodule attached to the right or to the left lobe. It is painless, and may remain unchanged for months. The nature of the case may only be determined by the development of a gumma elsewhere, or a tumor may arise in the epigastrium in a patient with slight fever, anemia, loss in weight, and the diagnosis of gastric carcinoma is made; or there may be a huge tumor the size of the two fists upon the surface of a greatly enlarged liver and the volume of the tumor may throw the practitioner off the scent. An important point in the diagnosis of these cases is the almost invariable association of enlargement of the spleen. Of course, there is nothing in the tumor itself which is of help in the differentiation from malignant disease. The syphilitic liver may be just as large and irregular as the cancerous, but there is rarely the rapidity of growth or the cachexia. (4) *Amyloid Liver*. In long-standing cases with necrosis of bones and in extensive gummatous disease the liver may be greatly enlarged with amyloid degeneration. The organ may be smooth and uniform, or there may be nodular irregularities due to gummata or other cicatrices. The spleen is usually greatly enlarged. Albuminuria is usually present with dropsy, and the general features of the cases are renal. Rolleston gives a case in which the liver weighed eight pounds and ten ounces. (5) *Cases Resembling Abscess*. The enlargement, the tenderness, the fever, and the slight jaundice, not unnaturally lead to the suspicion of suppuration, and if in addition to these there is a prominent tumor the suspicion becomes almost a certainty. The liver has been aspirated. Sometimes a gumma becomes secondarily infected and softens and forms an abscess. (6) Lastly, there are instances in which the great enlargement of the spleen and the diminished area of the liver suggest a primary blood disease, a *splenic anemia*, or, if the liver is reduced in size, Banti's disease. Coupland has reported a case in which the large spleen was removed, but the woman died from hematemesis. The liver was found to be syphilitic.

McCrae¹ has reviewed 56 cases of hepatic syphilis and draws the following conclusions: The disease presents a varied clinical picture. Loss of weight may be a prominent symptom, fever is common, the duration of the disease may be long, and periods of improvement are frequent. There are usually features suggestive of hepatic disease, of which general enlargement and the occurrence of nodules are the commonest. The diagnosis may be obscured by ascites and other conditions.

III. **Renal Syphilis.**—The most important renal complication is acute nephritis, a not at all uncommon event, but one to which comparatively

¹ *Amer. Jour. Med. Sci.*, 1912, cxliv, 625.

little attention has been paid. The French writers have for long recognized its importance, and Lafleur, of Montreal, brought the subject before the Association of American Physicians in 1896. Early in the nineteenth century the presence of albumin in the urine of syphilitics was noted, but it was attributed to the use of mercurials. Rayer pointed out that it occurred as a result of the disease itself, and this view has been amply sustained. There may be simply slight and transient albuminuria, such as occurs in the initial stages of any acute infection. In other instances the symptoms of nephritis become manifest within from two to four months of the initial lesion. In the majority of the cases it occurs with the cutaneous outbreak. The nephritis of later periods is of a different character, and depends upon amyloid change. The pathological changes described by Cornil resemble very closely those of scarlatinal nephritis.

The symptoms are those of acute or subacute nephritis. There is rarely any fever. The onset is insidious, usually without any pain in the back, and œdema is the first symptom noticed. It may be confined to the face and legs, or it may become general. The urine is diminished in quantity, smoky, contains blood, tube casts, and much albumin. After persisting for five or six weeks the albuminuria lessens, the dropsy disappears, and the patient makes a good recovery. A few cases have been reported in which death has followed in from fourteen to twenty-one days. Chronic nephritis is an occasional sequence. The nephritis may also occur in congenital syphilis. Chronic interstitial nephritis is met with in old syphilitics, and is, as a rule, the sequence of arterial changes. It is more commonly a patchy atrophy of areas of the cortex than a uniform general involvement.

Amyloid disease presents no special features.

Gummata.—The kidney is not often affected; when present the tumors are small, multiple, and rarely cause symptoms; even when a dozen or more pea-sized tumors are present there may be nothing to indicate their existence. In a few cases the kidney is the seat of enormous gum-mous tumors. Boldby¹ has reported the case of a woman, aged forty, with swelling in the right renal region. The kidney was enlarged, hard, and easily movable, and evidently the seat of a tumor of considerable size. A new-growth was diagnosed and the organ was excised. It weighed seventeen ounces and the surface was nodular on section. It cut like fibrous tissue and the surface presented an appearance exactly like that of a gummatous testis. All trace of renal tissue had disappeared. The patient recovered, but, as Boldby remarked, it must be borne in mind that a renal tumor of considerable size may be caused by syphilis, and it is probable that antisiphilitic treatment would have obviated the necessity for operation.

IV. Syphilis of the Circulatory System.—**BLOODVESSELS.**—Upon no system does the virus of the disease fall with greater intensity in all stages than upon the bloodvessels. It is safe to say that through the arteries syphilis kills more than through any other channel. Cerebro-

¹ *Pathological Society Transactions*, xlviii, 128.

spinal lues is largely a matter of arterial disease. The gummata often originate in or about the bloodvessels. The late arteriosclerotic changes leading to fibrosis are very often due to the toxins of the disease; but, above all, the association of aneurism with syphilis gives a place of first importance to its vascular aspects. Those acute old writers, Ambrose Paré and Morgagni, appreciated very clearly the frequency of arterial disease in syphilitic patients. In his classical chapter on aneurism there is scarcely a case in which Morgagni does not refer to the presence of syphilis. The very extensive literature is given in the papers of Benda and Chiari.¹

Gummata of Arteries.—The larger vessels are rarely the seat of distinct gummous tumors. Three changes are met with in the smaller bloodvessels:

1. *The Nodular Periarteritis.*—In this form many of the branches of the circle of Willis present nodular tumors, which may be from 3 to 5 mm. in diameter, oval in shape, firm and hard, often associated with gummous meningitis, or with numerous large gummata. The tumors are larger and firmer than in the nodular arteritis of tuberculosis. On section the nodular process seems to be almost entirely in the adventitia, sometimes with subintimal proliferation and with great narrowing of the lumen.

2. *Acute Gummatus Endarteritis.*—This, too, is most frequently seen in the cerebral arteries, but it has been described in the larger branches, and it is quite possible that the acute perforating ulcer of the aorta is of this nature. The lesion consists of a localized gummatus infiltration of the subintimal tissue, with softening and erosion leading to the production of aneurism or to perforation. This may occur quite early in the disease.

3. *Obliterative Endarteritis.*—This is seen most commonly in arteries of medium or small calibre. It may be limited to one or two vessels, as to one of the coronaries in which it is not at all infrequent, or to a posterior tibial. The endarteritis leads to a gradual narrowing and a final obliteration of the lumen. There is nothing specific in the process itself. It is a lesion met with in comparatively young persons with syphilis, which may be associated with gummatus lesions. An identical endarteritis may occur as a senile change or as a result of toxic agents.

Syphilitic Arteritis.—This is seen chiefly in the large branches, particularly the aorta, and is one of the most important of all the lesions of syphilis. It has nothing to do with the ordinary atheroma. While it may occur in persons above the middle period of life, it is most commonly seen in those under forty. It presents several special features: (a) The process may be limited to a small section of the aorta, an inch or so, for example, at the root, or a patch extending for a couple of inches in extent anywhere in its course. The intima in the rest of the extent may be quite smooth. The parts of the aorta most frequently

¹ *Verhandlung. der Deutsch. Path. Gesellschaft*, 1903, and Lubarsch und Ostertag's *Ergebnisse*, 1904 and 1906.

involved are the root, and the lower part of the thoracic and lower part of the abdominal aorta. The appearance differs very markedly from that seen in ordinary atheroma, particularly in the absence of calcification and of fatty degeneration and of areas of atheromatous softening. While in the early stage the intima may be smooth and the mesarteritis entirely microscopic, in the later stages the intima presents the appearance of what Marchand has called the scarring sclerosis. The intima looks wrinkled with linear depressions or little pockets, or there may be puckerings or scar-like fissures, sometimes arranged in a radial manner. The bottom of some of these depressions has a bluish tint, and held up to the light the vessel here looks translucent. (b) Microscopically the changes are very remarkable and consist in (1) extensive degeneration of the elastic fibres of the media, shown very well with the Weigert stain; (2) areas of small-celled infiltration, sometimes focal, sometimes linear. These two features of destruction of the elastic and of the muscular elements, with the widespread, small-celled infiltration often localized sharply in a media otherwise healthy, are the most characteristic microscopic changes. (3) The changes in the adventitia are often even more marked than in the media and consist of areas of round-celled infiltration which may be quite extensive and look like microscopic gummata. They frequently surround the arteries and they extend in linear form between the boundaries of the media and adventitia, or they may be traced in direct continuity with similar linear collections in the media. With this there is a marked obliterative endarteritis and endophlebitis of the vasa vasorum. (4) In the larger areas of small-celled infiltration giant cells are found and even patches of necrosis; and lastly, and this is an all-important point, Schmoll, Reuter, and others have found the spirochete in these lesions.

It is quite possible, of course, that other acute infections may lead to similar changes, and much discussion has taken place as to the specificity of those here described, but the evidence points strongly to the fact that syphilis is, at any rate, one of the most potent factors in the production of this form of arteritis, and the discovery of the spirochete seems to clinch the view which has been so well maintained by Chiari and others.

Syphilitic Aortitis.—Syphilis produces a characteristic lesion in the aorta which is responsible for most aneurisms, about 75 per cent. of the cases of aortic insufficiency in adults, many cases of dilatation of the aorta and a certain group of cases of angina pectoris. The *Spirochæta pallida* has been found in the wall of the aorta. This condition has interested a number of observers, the most recent of whom¹ has called attention to the following characteristics: The infection of the aorta probably takes place in the secondary stage, but symptoms often fail to appear until a number of years later. Syphilitic aortitis is probably a common cause for the presence of a positive Wassermann reaction in so-called latent syphilis. The early clinical features are a positive Wassermann reaction, precordial pain, slight dyspnoea, attacks of

¹ Longcope, *Archiv. Intern. Med.*, 1913, xi, 15.

paroxysmal dyspnœa and angina pectoris, cardiac hypertrophy, increased pulsation of the neck vessels and signs of dilatation of the aorta. The precordial pain, paroxysmal dyspnœa and angina pectoris are temporarily or permanently relieved by repeated injections of salvarsan, but in certain instances these symptoms, especially after large doses, may be aggravated for the first forty-eight hours after injection.

The Relation of Syphilis and Aneurism.—Morgagni seemed to be fully aware of an important relation between these two diseases. F. H. Welch, in 1876, called attention to the frequency of aneurism in soldiers and thought that at least 50 per cent. of the cases were associated with syphilis. Since then in the collections of statistics the percentage has ranged from 20 to 80. The more carefully the cases are looked into, the more accurately they are studied, the larger will be found to be the percentage of cases with the history of lues. One feature which has impressed the writers on the subject is that the age incidence of aneurism and of ordinary atheroma is different. In a large proportion the patients are in the third and fourth decade. The studies of Chiari, Benda, and others show that the type of mesaortitis here described is almost constantly present in cases of aortic aneurism. The recent experimental production of aneurism by the administration of adrenalin lends support to the view. The necrosis and degeneration is produced in the media, over which there may be a perfectly smooth intima; in places this may crack, and through the narrow fissure the blood passes and gradually a small aneurismal sac is produced. This is probably the sequence of events in the majority of cases of aneurism in man. The aortic wall is weakened in its most important coat by the destruction of elastic and muscular fibres, and during a sudden exertion, or spontaneously, the intima is split, with the formation of, first, a small aneurism which gradually increases in size. Of course, this does not exclude the origin of aneurism in a small proportion of cases from ordinary atheroma.

SYPHILIS OF THE HEART. The cardiac lesions of syphilis may be considered under the headings of endocarditis, fibrous myocarditis, and gummata.

Endocarditis.—Whether there is an acute endocarditis caused directly by syphilis is not yet settled. Taneff recognized a verrucose syphilitic endocarditis as a very rare form. Much more commonly it is a sclerotic form which may be either mural or valvular. The former is met with as thickened patches of the endocardium, chiefly of the ventricles, sometimes in direct connection with gummata in the myocardium. It is impossible to determine the specific character of an ordinary sclerotic valvulitis in a syphilitic subject. The cases most likely to be of this nature are those in which the valves are implicated directly in scarring of the mural endocarditis or in a patch of fibrous myocarditis. There is a very important group of cases in young syphilitic subjects who come under observation with angina pectoris, and who present signs of aortic insufficiency. The semilunar valves are involved with the root of the aorta in a specific mesarteritis and peri-arteritis. A strong evidence in favor of the luetic nature is the complete relief afforded by antisyphilitic treatment, the aortic insufficiency, of course, remaining.

Fibrous Myocarditis.—This is seen most frequently in the left ventricle and near the apex. In many cases it follows directly upon endarteritis of the descending branch of the anterior coronary artery. Unless gummata are present, or there have been well-marked signs of syphilis, it may not be possible to determine the specific character of the lesion. When extensive, it may lead to aneurism of the heart. In other instances the scarring in the myocardium is due to healing of small gummata. Widespread areas of fibrous myocarditis in syphilitic patients are most frequently the result of arterial disease.

Gumma of the Heart.—Stockmann, who has written a monograph on the subject (Bergmann, 1904), was able to collect 76 cases from the literature. The gummata may be small and multiple, or there may be a tumor as large as a walnut.

The *symptoms* of syphilis of the heart are indefinite. Sudden death is not uncommon. Of the 6 cases reported by Herringham all but 1 were brought into the hospital either dead or dying. Symptoms of dilatation are perhaps the most common. Attention has been directed particularly to two forms—the syphilitic variety of Stokes-Adams disease, in which there is either a gumma at the top of the septum, as reported in one of Keith's cases, or a syphilitic endo-arteritis. One of the cases reported by Erlanger had bradycardia and epileptiform seizures for a year or more, and recovered completely under specific treatment. The other group is the aortic insufficiency in young subjects, which may come on with attacks of angina pectoris. They also may be greatly relieved by appropriate treatment.

Syphilis of the central nervous system will be discussed under Diseases of the Nervous System.

The Tertiary Cutaneous Syphilides.—The tertiary syphilodermata are rarer than those of the secondary stage and vary less in type. They tend to become grouped or localized.

(a) The *tuberculous syphiloderm* is one of the earliest of the tertiary manifestations. The lesions appear first as small, brownish-red nodules, which gradually reach a considerable size and then undergo central disintegration. At the same time the lesion advances at the periphery by infiltration, and since this takes place more or less irregularly the ordinary picture is that of disintegrated tubercles with advancing crescentic walls of infiltration interspersed with superficial scars. The coalescence of adjacent nodules gives rise to the serpiginous and circinate syphiloderm. The eruption is usually confined to one part of the body, the forehead, the nape of the neck, the upper part of the back, and the serotum being the favorite sites. The differentiation from lupus vulgaris and lupus erythematosus may be difficult. On the palms and soles the tuberculous syphilide is a common manifestation. The lesions are often circinate and are accompanied by great thickening of the horny layer of the skin.

(b) The *gummatous syphiloderm* is the most characteristic tertiary cutaneous manifestation. It appears either in the skin or subcutaneous tissue, as a pea- to walnut-sized, rounded, painless nodule—fixed to the skin when cutaneous, movable under it when subcutaneous. The

gummata occur most frequently in the lower limbs and at the points where bone is directly covered by skin. The nodules increase in size; and, after a while, softening begins at the centre. The skin becomes reddened and finally may break, a sticky, tenacious, glairy fluid being discharged and a gummatus ulceration being formed. Gummata may, however, disappear without rupture, leaving slight traces behind them. They are usually few in number and occur late in the disease, but have been seen contemporaneous with the initial sore (Mauriac). Rhinoscleroma, carcinoma, and sarcoma have to be considered in the diagnosis of cutaneous gumma.

(c) The *ulcerative syphiloderm* is a later development either of the tuberculous or the gummatus eruption. The shape of the ulceration is at first that of the preceding lesion; but the marginal extension is usually irregular, and ulcerations of the most varied sizes and shapes are thus produced. The base of the ulcer is irregular and covered by secretion which dries into crusts, forming the pustulocrustaceous, the ulcerocrustaceous, or the rupial eruption. The ulcerations always result in scarring. They vary greatly in extent and number.

In the mucous membranes either the tuberculous syphiloderm or gummata may be seen. Softening and ulceration occur early, the lesion being most often seen in this stage. Its commonest site is the hard and soft palate; but it may also affect the tongue, pharynx, nose, vagina, etc. Tubercles and gummata also occur in the submucous tissue, where they form irregular, ragged ulcerations. The glossitis gummosa is a typical example.

The Quarternary Stage.¹—Certain pathological changes, neither exclusively nor necessarily caused by syphilis, bear to the disease a relation long unrecognized, but now undeniable. Fournier, who was one of the first to call attention to these changes, regarded them as of syphilitic origin, though not of syphilitic nature; and gave to the condition the name *metasyphilis* or *parasyphilis*. Many, although not all, occur long after the initial lesion; and the syphilis in its early stages may have been quite benign and have run its course without incident. Notable features are the proneness of parasyphilis to affect the central nervous system and the gravity of its prognosis. The more syphilis is studied, the more convinced one becomes that it is not the self-limited disease it was once thought to be; and the more prone one is to consider as an etiological factor the remote luetic infection of which there is a history in so many cases of the affections which have come to be known as parasyphilitic.

Moreover, recent studies of the disease have emphasized the frequency of parasyphilitic phenomena. Blaschko, from a study of life insurance statistics, reached the astonishing conclusion that one-third of all syphilis die later of tabes, general paralysis or aortic aneurism.

(a) **Tabes.**—Tabes is the type, *par excellence*, of parasyphilitic affections. It was in 1875 that Fournier first taught that tabes originated in

¹ The two following are the most useful works on this subject: (a) *Les affections parasyphilitiques*, by A. Fournier, Paris, 1894. (b) *Les affections parasyphilitiques*, by S. R. Hermanides, Haarlem, 1903.

the majority of cases from syphilis. Erb found 89 per cent. of a series of 600 cases of tabes to be syphilitic; Fournier about 90 per cent. of 750 personal cases; and Marie says, "For all practical purposes tabes is always syphilitic in origin." Certain of the cases of juvenile tabes have been shown by Strümpell and others to be the manifestation of hereditary syphilis. Added to the overwhelming clinical evidence as to the syphilitic nature of tabes are the results of recent serological studies; so that the question is no longer, Does a relation between syphilis and tabes exist? but, What is the exact nature of that relation? "Parasyphilis" and "postsyphilis" are no longer correct terms for tabes; the disease is a part of syphilis itself.

(b) **General Paresis.**—The etiological relation between syphilis and general paresis was first suggested by Esmarch and Jessen in 1857; but the idea has since been staunchly supported by others. The line of argument is much the same as in tabes and it is even more convincing; so that dementia paralytica must be considered among the parasyphilitic affections. Nearly 100 per cent. give a positive Wassermann reaction; and Noguchi has recently succeeded in finding the *Spirochata pallida* in the central nervous system of a number of cases of general paresis. Here again clinical facts seem to point also to a causal connection between juvenile general paralysis and hereditary syphilis.

(c) **Nervous Affections.**—There is a whole host of other nervous affections which have been described as parasyphilitic, but their discussion belongs rather to neurology and they can only be mentioned here. Quite important is the syphilitic neurasthenia, more particularly the syphilophobia, which inspires the afflicted patients with a colossal dread of the disease, interprets every trivial subjective sensation as a luetic manifestation, and assures its victims that all the most horrid events of syphilis are to be their portion and their offspring's. Parasyphilitic epilepsy is also a fairly well-established clinical entity; and besides these are to be mentioned hysteria, Little's disease, and hydrocephalus, among others.

(d) **Tongue.**—Parasyphilis frequently affects the tongue. It may take the form of fissures in persistent mucous patches or of recurrent herpes on the borders or dorsum of the tongue. But the common and serious lesion is buccal leukoplasmia, which often degenerates into carcinoma, and is supposed to be most frequent in patients whose mouths have been subjected to the irritation of tobacco. In this condition the epithelial layers are thickened and hornified, the intercellular spaces roomy and filled with round cells. Keratohyaline drops (stained an intense red with picrocarmine and the sure sign of hornification) are present. The onion bodies, seen in epitheliomata, are often found in buccal leukoplasmia. The adventitia of the vessels is thickened, there is proliferation of the connective tissue of the corium, and round-celled infiltration. The lymph and mucous follicles are also the seat of cell proliferation.

(e) **The Pigmented Syphilide** (*Syphilitic Vitiligo* or *Leucoderma*), already described, may be regarded as parasyphilitic because it is not peculiar to syphilis (homologous eruptions being the chloasma of pregnancy, cachectic melanoderma, etc.), and because it resists specific treatment.

(f) The list of parasymphilitic affections may be almost indefinitely extended if one includes all the diseases in which syphilis is often an etiological factor, but against which antiluetic treatment is useless. The importance of syphilis in the production of amyloid degeneration, of arteriosclerosis, and of aneurism has been referred to; diabetes insipidus is often associated with cerebral lues, and there are many more instances of suspicious association of this sort which might be mentioned.

Congenital Lues.—Effect of Syphilis on Pregnancy.—The first and most marked effect of syphilis on the fetus is the interruption of pregnancy. In 330 syphilitic gravidities studied by Kassowitz, abortion or premature delivery occurred in 40 per cent. and only 60 per cent. reached term. The nearer conception is to infection, the greater the danger of interruption of pregnancy. When many conceptions occur, however, in a syphilitic woman, the specific influence apparently “wears off;” the earliest pregnancies end in abortion, then dead children are born, then living children are prematurely delivered, then full-term syphilitic children, and finally full-term, healthy children.

In pregnant women who are syphilitic, hydramnios is also frequent. The fetus of a syphilitic woman either has macerated skin or, if born at term, presents the cutaneous lesions seen in adults. There are marked visceral lesions, particularly in the liver and spleen, which are much enlarged. The bones show the osteochondritis of Wegner, and the child has the pathognomonic “little old man” facies and the other characteristics of congenital lues to be described below. Placental changes are most marked when the disease is contracted by the mother early in her conception. The placenta is large, weighing sometimes one-quarter as much as the fetus. It is pale, œdematous, and either friable or firm. Microscopic examination shows placental cirrhosis with endo- and periarteritis and phlebitis of the chorionic villi. The umbilical cord also shows infiltration and vascular lesions.

The ill effects of syphilis on the children born of syphilitic parents may manifest themselves in three ways: (1) By faulty nutrition and various dystrophies; (2) by the actual signs of syphilis in the child at birth; (3) by the signs of the disease appearing some time after birth in a child born healthy.

1. **Dystrophies Syphilitic in Origin.**—The inaptitude for life transmitted by luetic parents to offspring, even when no actual syphilitic lesion is demonstrable in the child, may show itself in the intra-uterine death of the fetus. When, however, the child reaches term, even in absence of definite signs of syphilis, the luetic dystrophies are often seen. Some of the children are born small, have no resistance to gastro-intestinal and other infections, and die early. Others survive; but they remain small, atrophic, and infantile, both in physique and intellect, have very slight resistance to infections, and are particularly subject to rickets. Faulty development and diminished resistance are prominent characteristics. Numerous malformations may be added; but, although these are often seen in the children of luetic parents and seem to be syphilitic in origin, if not syphilitic in nature, most of them may be and frequently

are due entirely to other causes. These malformations usually affect the cranium. Asymmetry of the skull is often seen; large frontal bosses are not uncommon; and microcephaly and other variations of the head, both in size and shape, are observed.

Other characteristic deformities are seen in the face and mouth; for example, the flattened nose and the vaulted palate. Scoliosis and spina bifida are not infrequent. Polydactylism, syndactylism, congenital luxation of the hip, and flat-foot are some of the deformities of the limbs seen in the children of luetic parents. The heart valves are often faulty; congenital hernia is not rare; malposition of the viscera is occasionally observed, and incomplete development of testicles, breasts, and ovaries is sometimes seen. Retardation of intellectual development may be very slight, but quite often the children are slow in their mental grasp and lack attentiveness and memory; in some cases the children are congenital idiots. Deaf-mutism, deafness, strabismus, keratitis, malformation of the iris and other ocular structures are some of the deformities affecting the organs of special sense. One of the most characteristic malformations is seen in the teeth; this deformity was studied chiefly by Jonathan Hutchinson, and the "Hutchinsonian teeth" are regarded as one of the very important stigmata. The change affects the median upper incisors of the permanent set of teeth. The teeth themselves are stunted and peg-shaped, their lateral borders being curved, and their axes usually converging from base to edge. At the free-cutting border there is a single, broad, shallow, crescentic notch, or semilunar excavation. It persists for some years; but is finally obliterated by wearing down of the teeth. These changes described by Hutchinson are quite definite, and it is improper to call any malformed syphilitic teeth, "Hutchinsonian teeth." The typical changes may, however, be absent and other malformations (not themselves peculiar, as the Hutchinsonian teeth are, to syphilis) may be seen. Transverse grooves and depressions are among the commoner changes, the latter sometimes taking the form of the cupuliform atrophy of Parrot. Simple microdontism is sometimes seen.

2. Early Congenital Syphilis (*Syphilis héréditaire précoce*).—This is the most frequent form. The signs and symptoms are characteristic and the diagnosis is usually easy. Sometimes the disease is manifest at birth, but usually the child is born healthy and thrives until about the sixth week; occasionally the symptoms appear first about the sixth month. The typical facies described by Trousseau presents the following features: The skin is yellowish, the expression wretched, the eyelashes are wanting, the hair of the head scanty, and patches of alopecia are present; later, the appearance becomes the well-known one of a "little old man." The facies of Trousseau may be absent. The appearance of actual symptoms may be preceded by a period of restlessness and wakefulness. One of the first symptoms observed is the characteristic rhinitis known as "the snuffles;" this is a coryza with serous discharge, the formation of crusts, and resulting in respiratory obstruction. The child usually at this time begins to nurse badly and nutritional disturbance supervenes. Ulceration and necrosis of the nose, with the formation of the saddle-

shaped deformity, may occur. Fissures or rhagades appear at the corners or the free borders of the lips, increasing the wretched appearance of the child and greatly adding to the danger of contagion on the part of the nurse. Anemia is present. The child goes from bad to worse; it suffers from malnutrition and often succumbs to cachexia. Many of the children are carried off by intervening acute infections, particularly bronchopneumonia and enteritis. Among good hygienic surroundings the prognosis is fair; otherwise it is grave, and in foundling hospitals the children practically all die. The glands are usually not enlarged; but a whole host of cutaneous lesions, including most of those seen in syphilis of adults and certain others peculiar to the congenital form, appear. Their severity is a clinical characteristic.

The *roseola* is usually wanting; but a yellowish-red, maculopapular erythema, beginning on the buttocks and thighs and extending to trunk and face, is sometimes seen.

The *psoriaform syphilide* is very characteristic. It consists of bright-red or copper-colored, infiltrated areas on the palms of the hand and soles of the feet, covered by white, dry scales, which are easily detached, leaving a collarette at the periphery. It corresponds to the psoriasis palmaris and plantaris syphilitica of adults.

The *erythema*, when situated about the body orifices, is usually accompanied by *rhagades*. These are true ulcerations, which may leave indelible scars, particularly characteristic about the lips and chin.

Mucous patches occur in the mouth and about the lips; but they show a predilection for the intergluteal groove, the perineal, genital, and genitocrural regions. This may be due in part to the constant irritation by urine and feces in these sites. There is, however, very little tendency to condylomatous overgrowth, as in adults. Patches are also seen back of the ears and near the nose, where they are often covered by crusts.

Pemphigus neonatorum is the most characteristic of the cutaneous lesions. This syphilide is most often situated on the palms of the hands and soles of the feet. It may be present at birth, or, if appearing later, it begins as a bluish-red infiltration; the epidermis is soon raised and vesicles and bullæ are formed. Sometimes, however, there is no liquid present. The lesions are 2 mm. to 1 cm. in diameter. The epidermis is white, as if macerated, and lies in folds; below, the skin is reddish, wine-colored. The serous exudate soon becomes purulent; the vesicles become tense and are either absorbed or burst, leading to purulent ulcers, which are often serious. In malignant cases there is extensive destruction of the skin, with gangrene, necrosis, and, not infrequently, death.

Hemorrhagic Exanthemata.—Syphilis is a well-recognized cause of hemorrhage in the newborn and not infrequently this occurs subcutaneously (syphilis hemorrhagica neonatorum). The hemorrhages may be subcutaneous or submucosal; sometimes they occur about the umbilicus. Of 3364 children studied by Wilson at the Philadelphia Lying-in Charity, 10 died of hemorrhage attributed to syphilis. Reduced coagulability of the blood and increased arterial tension in the newborn are the causes assigned by him. Jaundice is practically always present in some degree.

Aene syphilitica, *impetigo syphilitica*, and *ecthyma syphilitica* are three self-descriptive exanthemata more or less characteristic of the congenital form of lues. The *poorly nourished skin* of children afflicted with hereditary lues is also subject to many skin affections not themselves specific. Eczema intertrigo is, for example, quite common; and suppuration and destruction of the nails are not infrequent.

Bony changes are frequent and characteristic. The dystrophies of the cranium, particularly the frontal protuberances, have been mentioned. In the limbs they often manifest themselves in the syndrome of Parrot (syphilitic pseudoparalysis of the newborn). This is characterized by immobility, pain, bony swelling, and sometimes crepitation at the epiphyseal line. There is no true paralysis, the muscles reacting to faradism and galvanism. It usually affects only one limb, but sometimes two. It may be the first sign of congenital lues; but more often appears in the third or fourth month.

Osteochondritis syphilitica, first described by Wegner, is highly characteristic of congenital lues. Its site is the boundary between diaphysis and epiphysis of the long bones (upper end of the tibia and both ends of the femur particularly) and between bone and cartilage in the ribs. Three stages are recognized. In the first there is marked proliferation of cartilage cells at the boundary of the diaphysis, forming a zone recognizable macroscopically between diaphysis and epiphysis. Within this zone ossification is irregular and retarded. In the second stage proliferation of cartilage cells advances and there is further irregular ossification at the epiphysis. In the third stage one finds bulgings of the cartilage, with thickening of perichondrium and periosteum. The cartilage forms a broad, irregularly limited zone; the portions next the spongiosa consist of a pus-like, semifluid mass. Epiphyseal separation may occur.

Visceral lesions are observed in practically all the organs of congenitally syphilitic children. Many of them are without characteristic symptoms; diarrhœa and vomiting occur, but they are not pathognomonic. Involvement of the testicle is, however, particularly characteristic; and orchitis with exudative vaginitis in an infant is always suggestive of lues. It usually ends in sclerotic atrophy. The enlargement of liver and spleen are also of clinical importance from the aid they give to diagnosis. The former is regular, smooth, and very large, reaching sometimes to the iliac fossa. It is cirrhotic, but the cirrhosis is usually unaccompanied by circulatory changes or icterus. The large, palpable spleen is also of diagnostic import. Affections of the eye are seen in the early form of hereditary syphilis, but interstitial keratitis is much less frequent than in the late form.

3. **Late Congenital Syphilis** (*Syphilis héréditaire tardive*).—This form, especially studied by Hutchinson and others, has been clinically well recognized only in comparatively recent years. Its manifestations were formerly either regarded as those of acquired syphilis or dismissed as "scrofulous." It appears usually about the time of the second dentition or at puberty, and is most frequent in those who have shown signs of the early form in infancy. It occurs also, however, in patients whose childhood has been free from disease. Its manifestations are not often

seen after the twenty-eighth year; but a terminal time limit is, of course, difficult to set. Any organ in the body may show syphilitic manifestations of a gummatous, sclerous, or sclerogummatous type; but the following are those most often affected: the eyes, the bones, the skin, the throat, the pharynx, the brain, and the ear. One of the most important changes is the almost pathognomonic interstitial keratitis. This usually occurs between the eighth and fifteenth year, and begins as a diffuse haziness near the centre of the cornea of one eye. It is accompanied by some irritability of the eye and by dimness of vision. When looked at more closely the corneal haziness is seen to consist of discrete, punctate deposits within the cornea itself and not on its surfaces. In a few weeks the whole cornea becomes involved, takes on the appearance of ground-glass, and is surrounded by a zone of ciliary injection. Photophobia becomes a symptom and involvement of the opposite cornea takes place. The vision is quite dimmed; but soon the condition begins to improve and the cornea clears slowly. If the case is treated early, the prognosis is fair and is inversely proportional to the degree of photophobia. Recovery is, however, always slow and, at best, imperfect.

The cutaneous and mucous lesions of late congenital syphilis in general resemble those of acquired lues. Fissures and rhagades occur about the mouth. Changes in the bones are a marked feature; bosses are seen on the skull, and hyperostoses on the long bones. The sabre-shaped tibia is particularly characteristic; here the bone is much bowed and is increased in volume by a chronic osteoperiostitis accompanied by gummata. The latter often break down and ulcerate. Arthropathies are occasionally seen, particularly a form of synovitis which resembles white swelling; and a special form of symmetrical synovitis of the knee has been described by Clutton.

In typical cases the whole clinical picture is characteristic. The patients are small and poorly developed; the skin is of an earthy paleness; the forehead is prominent, the frontal eminences marked, and the skull asymmetrical; the bridge of the nose is depressed and its tip *retroussé*; there are cicatricial stigmata of the skin and mucosæ, and striae about the mouth; there is the presence of the Hutchinsonian triad (pathognomonic alterations of the teeth, interstitial keratitis, and disturbances of hearing), there are signs of infantilism (slender physique, undeveloped testicles, rudimentary beard, and pubic hair); there is glandular enlargement often mistaken for tuberculosis; and finally there is arrested intellectual development. Further confirmation of the diagnosis may be obtained by inquiry into the family history, which will often show a high mortality or a high percentage of abortions; and, by confrontation, revealing the source of the disease in one parent or both.

Diagnosis.—The Wassermann Reaction.—It was the fundamental discovery made by Bordet and Gengou of the principle of complement deviation which led Wassermann to study the blood-serum of syphilitic patients and to devise the important biological test which bears his name. The reaction depends on the capacity possessed by the blood-serum of syphilitic patients to fix complement in the presence of extracts of syphilitic tissue, or certain other alcoholic extracts. This fixation of

complement is tested for by the use of a so-called hemolytic system, which consists of red blood cells and a serum capable—in the presence of complement—of hemolyzing them. In making the test, an extract of known syphilitic material and the blood serum of the patient to be tested are mixed in a test-tube. Fresh guinea-pig serum is added and the mixture incubated to allow complement-fixation to occur. The hemolytic system, which requires complement for the completion of the hemolysis, is next added. If the serum to be tested is not syphilitic, complement is not bound and hence is available for the use of the hemolytic system; hemolysis, therefore, proceeds, the red blood cells are destroyed, the mixture becomes red in color, and the test is negative. If, on the other hand, the serum is syphilitic, complement is bound, hemolysis inhibited, the red blood cells not destroyed, the mixture not reddened, and the test is positive. This test, while neither absolutely specific nor absolutely constant, is one of the most valuable of the biologic reactions. As to its specificity the following statements may be made: (1) A positive reaction occurs in syphilis, in the tuberculous form of leprosy, and in fresh malaria. (2) In other fevers and wasting diseases a partial deviation of complement may occur, but these reactions (though sometimes reported as positive) are really negative. Here belong the cases of scarlet fever with "positive" reactions. (3) The evidence as regards the Wassermann reaction in other trypanosomal and spirochetal diseases is not yet complete. (4) Most of the positive reactions in non-luetic conditions date from the early days, and are attributable to faulty technique. They are becoming less numerous as the technique improves. In a large early series about 1.8 per cent. of normal patients gave a positive reaction.

The general opinion is that in syphilis a positive reaction never appears before the fourth and only seldom before the fifth week. Reasoning from monkey experiments, Neisser and Bruck held that a positive reaction was a sign of a generalization of the infection, but it seems likely that in man such a generalization has occurred before the appearance of the primary lesion. In the secondary and tertiary stages if florid symptoms are present and the patients have not received treatment a positive reaction is obtained in 98 to 100 per cent. of the cases. In the "latent" cases a smaller percentage of positive reactions is obtained; but some of the negative reactions in these cases may be due to treatment undergone and forgotten. A clinical diagnosis of the local condition must, of course, always be made; a positive Wassermann reaction almost certainly means that syphilis is present; but the lesion in question may be due to something else.

A negative reaction has little diagnostic value in the primary stage and in the symptomless stage of congenital lues. But in untreated syphilis, repeated negative reactions (particularly if the test is made with a variety of antigens) are very valuable indeed. How long a Wassermann reaction should remain negative in order to be sure that cure has been effected cannot be said; but even so, the course can be followed with far greater surety if the Wassermann reaction be taken, than if we rely purely on clinical data. Reactions which remain positive in spite of

treatment, indicate a severe type of infection, and probably a number of the patients showing this condition will develop *tabes* later.

A positive Wassermann reaction means syphilis and indicates that the treatment should be continued until a persistent negative reaction is obtained. In the secondary stage, a positive reaction without symptoms means a recurrence of the disease, and here (as indeed throughout the course) the reaction should be regarded as the criterion for treatment. Treatment may be stopped on a persistently negative Wassermann reaction, but subsequent control tests should be made every two years. In late cases with a positive reaction but no symptoms it is difficult to know what to do; in general, the ideal should be to convert all positive reactions into negatives.

Wassermann thinks that the test should be made on all pregnant women, particularly in institutions, and is very hopeful that early detection of maternal infection may make it possible to prevent fetal infection, or even to cure it, through treatment of the mother.

The Wassermann reaction has proved of great value in demonstrating the syphilitic nature of certain "parasyphilitic" conditions; and has also thrown light on the disease in prostitutes. A study of prostitution in Cologne showed that while only a small number of the women presented active signs of syphilis, about 85 per cent. gave a positive Wassermann reaction. This observation may prove important in the effort to secure more efficient medical supervision of prostitution.

Cutaneous Reaction in Syphilis. The production of a cutaneous reaction by von Pirquet and others in tuberculosis suggested the application of this method to syphilis. For this purpose Nicolas, Favre, Gautier, and Chartet used a glycerin extract of the liver from cases of congenital syphilis, sterilized by heating to 115° C. To this extract they gave the name of "syphiline." Intradermic inoculation gave better results than cutaneous. The results were compared with those of the Wassermann reaction, and agreed (intradermic) in 42 out of 50 cases. In 2 cases of undoubted syphilis a positive intradermic reaction was obtained when the Wassermann test was negative. Noguchi has reported similar experiments with an emulsion or extract (luetin) of pure cultures of *Treponema pallidum*. He concluded that the skin reaction was more constant in the tertiary and latent forms, the Wassermann reaction more constant in the primary and secondary stages. Mothers who have borne syphilitic children usually give a positive skin test.

Prognosis.—Syphilis is a curable disease. It is not, however, *always* cured even by the most efficient treatment; and there is unfortunately no way of determining with exactness whether treatment in a given case has been sufficient to warrant us in a dogmatically favorable prognosis. We have only empirical results to go upon; but the clinical records of large series of cases carefully studied over long periods of years justify the following conclusions as to the outlook for a luetic patient:

1. In general, the prognosis for the average case is good with careful treatment and bad without it. This holds for the secondary phenomena, for tertiarism, and for the transmission to progeny.

2. No deduction as to the virulence of the disease is to be drawn from the character of the chancre; phagedenic sores may introduce a mild syphilis and herpetic chancres a malignant one. Nor do the secondary symptoms *per se* give us any indication of the future.

3. The prognosis improves with the promptness of the institution of treatment and seems to depend pretty directly on the vigor and intensity of the early mercurialization. The secondary period, if the sore has been positively diagnosed and treatment promptly begun, is as a rule only manifested by a few benign symptoms; on the other hand, cases first treated in the tertiary stage are difficult and often impossible to cure.

4. The frequency of tertiary symptoms, other things being equal, is inversely proportional to the adequacy of treatment received. The frequency of these lesions, and of the parasyphilitic phenomena, should now become less, since the presence of "latent" syphilis can be detected by the Wassermann reaction and the late features forestalled by treatment.

5. A patient who has received the thorough treatment outlined below is entitled to consider his disease cured and himself a safe husband and father. We cannot, however, *guarantee* that no syphilitic or parasyphilitic phenomenon will manifest itself. * We can only say that such an occurrence is extremely improbable. "Neither the dose," said Ricord, "nor the pharmaceutical preparation, nor the duration of treatment, confer immunity with certainty or guarantee the complete and radical extinction of syphilis." For this reason a patient who has had syphilis should never be dismissed from observation; and he should be advised of the importance, in case of future disturbance of health, of informing his physician of his syphilitic antecedents.

6. Three types of syphilis may be recognized, according to course and prognosis. *Benign syphilis*, which is even occasionally seen in untreated cases, occurs most commonly in women. Here the initial lesion, a mild sore throat, a moderate roseola, and an adenopathy, perhaps with headache, make up the entire symptom-complex. *Normal syphilis* shows well-marked but not severe symptoms throughout, and the manifestations are quite amenable to treatment. After a certain time, during which a number of relapses and exacerbations occur, the disease ends, although parasyphilitic phenomena may later appear. *Malignant or galloping syphilis*, less frequent now than formerly, presents either the normal manifestations in severe, frequently recurring, and obstinate form, or else violent, often rapidly fatal tertiary manifestations early in the disease. The skin eruptions are ulcerative and pustular; cachexia is marked; gummatous lesions are extensive and occur early, and the internal organs are rapidly involved.

7. Congenital syphilis offers in general a very bad prognosis. The average mortality is probably about 75 per cent. Kassowitz states that one-third of all syphilitic infants die *in utero*, and of the remainder 34 per cent. succumb during the first six months of life. Here, again, treatment affects the prognosis wonderfully; according to Etienne 95.5 per cent. of living syphilitic children die if untreated and only 10 per cent. if properly cared for.

Syphilis and Marriage.—The most accurate method of determining whether a patient may or may not safely marry is by a study of the Wassermann reaction. In most cases, if the patient has undergone thorough treatment and has remained without symptoms for at least one year after treatment has ceased, he may be regarded as non-infectious.

Syphilis and Insurance.—The relation of syphilis to the problems of longevity gives this disease great importance from the standpoint of life insurance. It is very difficult to estimate the percentage of deaths actually due to syphilis; but the vital statistics published by the United States Census Bureau make it seem probable that the fatality is about 2 per cent. (Hyde). Runeberg, of Helsingfors, on the other hand, found that 11 per cent. of 734 deaths of insured persons were due to diseases resulting from syphilis; and that if certain apoplexies, probably syphilitic, were included the syphilitic mortality was 15 per cent. of the total, being second only to tuberculosis which caused 21 per cent. of the deaths. These figures assume added importance when it is remembered that they represent the facts existing among the insured—that is to say, the most vigorous portion of the population. Chronic alcoholism, long-continued tobacco narcosis, extreme fatigue, severe affliction, poverty, and the stress of anxiety are well-known contributing factors to the serious effects of syphilis. The diseases most commonly causing death after syphilis are affections of the circulation, general paralysis, diseases of the central nervous system, chronic nephritis, and aneurism.

The damage wrought by syphilis consists, however, chiefly in its lowering the standard of average health, paving the way for other diseases and possibly laying the foundation for mental degeneration and alienation. The expectation of life after acquired syphilis is in large measure affected by the inherited tendencies, the habits of life, and the environment of the individual. The longevity prospects are undoubtedly better for women than for men. The ideal applicant for life insurance who has suffered from syphilis should have had active and unmistakable symptoms early in life; he should have had, after efficient treatment, several years' exemption from all evidences of infection; he should have an excellent family history, particularly as regards nervous diseases; and he should lead a life relatively free from strain, excess, indulgence in alcohol and tobacco. Most insurance companies require that four or five years shall have elapsed since the disappearance of the last symptoms of the disease; and no applicant who has had syphilis is given a policy which will keep him on the company's books after his fifty-fifth year. The frequent occurrence of arteriosclerosis in middle life among those who have had syphilis suggests the possible practical value of studying the blood-pressure of these applicants for insurance with regard to increased arterial tension at the time of application. (Hyde.)

Prophylaxis.—There are many striking things about syphilis, but none is more striking than its persistence in spite of knowledge complete enough to stamp it out. It is a disease almost unparalleled in the extent and intensity of its ravages; it is the subject of popular dread; yet it is both preventable and, within limits, curable. The close connection of the problem of syphilis with the problem of prostitution—and particularly

with that of clandestine prostitution—makes it essential for the physician to familiarize himself with the hygienic significance of this industry and with the methods that have been adopted to keep it within bounds. Prostitution is the source of the disease; it is prostitution that keeps it in circulation; and no problem of greater importance to the commonwealth could be presented to the State. It cannot be said that the efforts of the State to comprehend or solve the problem have met with brilliant success. Rigid State control, with medical inspection; simple State regulation; and the establishment of brothel streets (as in Bremen) are among the methods that have been tried. Their various merits cannot be discussed here. Opinions about them are varied.

The question of State regulation of prostitution, it must, however, be insisted, is really one of the minor problems connected with the problem of the prophylaxis of syphilis. Governmental supervision deals, even under the most ideal conditions, with an almost negligible fraction of the total prostitution, and from the very nature of the case leaves untouched the clandestine prostitution which is spreading disease. It is, furthermore, absurd to ask much of it, when it is remembered that law is only effectual as an expression of the predominating opinion of the commonwealth; and to expect, as has been expected, that State regulation subdue prostitution in countries where the mistress is not simply a tolerated but a well-recognized and accepted personage, where promiscuous intercourse not only thrives, but has actually created for itself a literature, where the marital tie is regarded in the loosest way, is like sowing weeds and then asking for a law that no weeds shall grow.

We have then to consider those aspects of the public hygiene of syphilis not directly concerned with the attitude of the State toward prostitution.

Public Prophylaxis Concerned with Syphilis Itself.—(a) It has been suggested that the disease be made a reportable one and that treatment be obligatory. Aside from the very large problems which this procedure would create as to a physician's right to reveal a professional secret of this nature, it seems quite certain that a regulation of this kind would rather hinder than promote proper treatment. Enforced publicity would certainly lead to the concealment of syphilis, and many cases now well treated would go untreated.

(b) The establishment and maintenance of proper institutions for the study and treatment of venereal diseases is a crying need everywhere; and the commonwealth can do nothing better for the common weal in the matter of syphilis than by making this necessary provision. This is a part of the fight against the disease which has been woefully neglected; it is a part which should receive the support of every well-informed physician, as offering a well-grounded hope of accomplishing much in the attempt to eliminate the sources of infection and to diminish the miseries of the already contracted disease. The cure for syphilis is known; if it is not applied, the fault lies with the community which chooses to make no use of its knowledge; and of this blame the medical profession must accept a large share.

(c) *Antisymphilitic Vaccination.*—Experiments with this method of prophylaxis have not been very satisfactory and the procedure must

develop greatly before any State interference of this sort promises to accomplish what compulsory vaccination against smallpox has brought about. Various sera have been used: blood-serum from syphilitic subjects in the secondary or tertiary stage, serum from heredosyphilitic subjects, serum from the secretions or pathological liquids of syphilitic subjects, serum of animals inoculated with various syphilitic products. Noguchi's successful cultivation of the spirochete of Schaudinn may facilitate the study of this question.

Public Prophylactic Efforts Concerned with Society and its Institutions.—Procedures of every sort have been suggested according to which the prophylaxis of syphilis was to be strengthened by some change in the legal attitude of the State toward the disease or by an alteration in the institutions of Society.

(a) Penalty for the transmission of syphilis has been proposed by some as a necessary and important step in the attempt to destroy it.

(b) Should the transmission of syphilis from husband to wife or from wife to husband constitute grounds for divorce? This is a difficult question which belongs rather to law than to medicine; yet it cannot be disregarded in considering the prophylaxis of syphilis. The hideous injustice to which a husband or a wife submits when he or she is knowingly and voluntarily infected by the other party, tempts one to provide legal redress for the predicament. Yet the procedure is a dangerous one; its application would present great practical difficulties, and it is doubtful if it would often be taken advantage of by the injured party.

(c) It has also been urged that a certificate of health as regards venereal disease be required before marriage permits are issued, and in some communities steps have been taken in this direction. Upon one point there can be no doubt. It is the bounden duty of every physician to use every means in his power to prevent marriage between people with venereal infections. He should absolutely forbid his syphilitic patients to think of this step until they have undergone proper treatment, and he should enforce this command with complete information as to the misery sure to result from such a marriage.

(d) Sanitary examination of men. (1) Such an examination, together with obligatory treatment, already obtains among certain government employees, as, for instance, in some armies and navies. Diday maintained that it should apply to all government servants, and the method of attacking syphilis by requiring all civil service employees to undergo examination has been strongly urged. It has also been suggested that all public wards (tramps, beggars, and prisoners) should be submitted to examination for syphilis. (2) The examination of customers on their entrance to brothels has been seriously urged by certain writers as a promising procedure in preventing syphilis. The idea is no new one. As early as 1430 there was a regulation requiring such an examination in London, and Diday was a strong supporter of the idea. It was tried for a while in Hamburg. The scheme is, of course, quite out of the question, for it would be perfectly impossible to find reputable physicians who would give their time to such business, and in the hands of any but such physicians it would lead to all sorts of graft and abuse. Further-

more, as Ricord showed, it would simply result in an increase of free prostitution: "Aside from the difficulties of such an arrangement, the dangers which one wished to prevent by it would be increased, for instead of falling into a sewer which the police could cleanse, the filth would go elsewhere."

(e) It is notorious that venereal diseases furnish a large percentage of the material of charlatanism. In the case of syphilis the insufficient and unintelligent, if not actually dangerous, treatment which results is a definite menace to public health, and war on charlatanism is therefore a distinct part of the prophylaxis of syphilis. Nowhere can neglect or ignorance bring greater misery, and most often to the innocent, than in the case of this disease; that its care should be in competent medical hands is therefore essential to the public health. Provision for its treatment in adequate venereological dispensaries is one phase of this prophylactic measure; but legal provision against the industry of quacks, a provision to which the public, with strange neglect of its welfare, is indifferent or even hostile, is an equally important feature.

(f) There are certain industries (glass-blowing is one of them) notoriously dangerous in the transmission of syphilis; and it seems to be well within the power and duty of the State to see to it that proper hygienic supervision is exercised. That vaccination should be under rigid oversight in this respect goes without saying; and the possibility of infection by surgical or dental instruments is one that has but to be mentioned in these days of careful technique. One should insist, however, on the very great care necessary in venereological dispensaries where chancres are being constantly handled and circumcisions frequently done, for this operation has more than once been responsible for the transmission of the disease.

(g) Education, the sovereign balm in so many other instances, offers the greatest hope. Here is a disease bringing untold misery to a large proportion of the community, rendering great numbers of citizens inefficient, and transmitting its calamities to wholly innocent parties. It is a disease the phenomena and far-reaching miseries of which are known with certainty; it is a disease which can be perfectly well avoided; it is a disease which, when contracted, can be greatly limited both in its early manifestations and its late effects. Yet it is a disease about which even the educated classes are wholly uninformed or woefully misinformed; while the masses depend for their information on the unintelligent mouthings of alarmist quacks.

1. *Education of the Medical Profession.*—Students are rarely well instructed in syphilis; they are almost never thoroughly instructed. "This explains," writes Fournier, "why medical men mistake chancres and mucous patches for something else; why they give syphilitic infants to the care of a healthy nurse, or inversely; why they regard syphilis as cured after a few months or even weeks of treatment, and why they permit marriage to uncured syphilitics." In no way, indeed, does the public health suffer more when medical errors are made than it suffers if the errors be made in regard to syphilis; and these are errors which might be avoided by adequate attention to the subject in medical curricula.

2. *Education of the Laity.*—This procedure is a delicate and difficult one. Certain suggestions may, however, be made as to possibly valuable educational undertakings.

(a) The first need is that the dangers of syphilis, about which the laity has the vaguest ideas, become matters of public knowledge. It is, of course, idle to expect that such knowledge would entirely protect the public from contagion; for those who are to be deterred from debauch by no consideration of public or private hygiene would continue to contract and to spread the disease. There are, on the other hand, certain people who are absolutely protected from danger by a thorough knowledge of it; and it is the duty of the medical profession to see that such persons, however small a part of the community they form, do not have to purchase their knowledge at the price of experience. Just how this knowledge is to be spread is a matter for consideration on account of the unique delicacy of the task. No doubt one of the functions of a venereological dispensary is that of instruction; and it would probably be useful to have printed guides distributed from these centres in somewhat the same way as is now done for tuberculosis.

(b) It is also in the interest of public health that the community should understand the dangers of prostitution. Instruction in this matter, by reason of its difficulty and delicacy, offers hope of doing good only when given with the utmost wisdom. Yet the opinions of students of the question and the success of modest efforts already made are united in encouraging us to hope that something may be accomplished by this form of education in the future.

(c) It is incumbent on the medical profession to keep itself informed and to instruct the public as to the danger of innocent syphilitic contagion. Nothing can be more tragic than the disease acquired in this way, and in a large number of instances information and reasonable care would have entirely prevented it. The danger of transmission by wet-nurses and by many of the contacts of every-day life should be known to all men.

(d) The close association between alcoholic abuse and the contraction of venereal disease being an absolutely established fact should, in the interest of public health, be more widely appreciated.

(e) Lastly must be mentioned the close association between the prophylaxis of syphilis and many social reforms. This is not the place to go into these matters in detail; but there can be no doubt that public hygiene demands attention to them on the part of medical men. Prostitution, the great source of the disease, is at present a part of the social fabric; and it exists, partly at least, because of the injustices of society. No movement therefore which makes for improved industrial and hygienic conditions can fail to be of service in the fight against syphilis.

The Private Hygiene of Syphilis.—There can be little doubt that the physician has a distinct duty to fulfil to his patients in explaining to them certain elementary hygienic details which cannot well be publicly considered, and which do not enter into the prophylactic campaign of the State. There is first the question of continence, and here the physician

dare teach his patients but one thing, namely, that continence, no matter how difficult, is the relation of greatest safety for the individual and for society and is not detrimental to health.

The experimental work of Roux and Metchnikoff has shown that mercurial inunctions at the site of inoculation with the syphilitic virus are effective in preventing the disease if applied within eighteen and one-half hours of the time of infection, though if applied later they are without avail. Neisser's observations seem to indicate that bringing the body immediately under a general mercurialization has no prophylactic value. In the United States Navy rigid prophylactic measures (inunctions) are now enforced and the results seem to have been, on the whole, satisfactory.

The Prophylaxis of Hereditary Syphilis.—This is the most tragic form of the disease, and it is therefore unusually gratifying to know that much can be done toward preventing it. The most certain prophylaxis consists, of course, in proper treatment of the parents before marriage. In statistics compiled by Fournier, it has been shown that the infantile mortality of the issue of subjects whose syphilis has been properly treated is only about 3 per cent. In 45 pregnancies, however, occurring after the marriage of untreated syphilitics, the mortality was 82 per cent.

We are here concerned rather with the question as to whether there is any hope of protecting the fetus by treating the mother. It has been shown that mercury and potassium iodide pass from mother to child through the placenta, and there is evidence that salvarsan is similarly effective. This treatment is therefore rational, and, as a matter of fact, it has produced excellent results. Women, for instance, whose previous pregnancies had been disastrous, have frequently had normal pregnancies when specific treatment was instituted. Treatment to be effective must be begun in time. "After the fifth month it is too late," says Pinard. Mercury is the drug to be given, and is best administered in the form of the proto-iodide pills. The fetal dose cannot, of course, be accurately gauged, but about gr. 1 is usually a sufficient dose. The treatment should be continued during the whole pregnancy. Pinard advises continuous treatment, but others prefer the intermittent method—twenty days' treatment and ten days' rest every month.

Treatment. Initial Stage.¹—It is usually the appearance of the chancre which brings syphilitic patients for treatment. In many instances, it is true, the chancre is entirely overlooked or neglected and the patients are first seen with secondary or tertiary symptoms; but as a rule the physician's therapeutic problems begin with the chancre itself. The idea that syphilis might be extinguished *ab ovo*, by treatment directed at its initial lesion, has always been an attractive one; and blockading, excision, and cauterization of the chancre have been practised with enthusiasm. By general consent, however, the practice has gradually

¹ Fournier's incomparable *Treatment of Syphilis and Prophylaxis of Syphilis* are now published in English translation (Rebman Co., 1906). Nothing better exists on these subjects.

been abandoned for the reason that its failures far exceeded its successes, and that the chancre itself indicates not a localized, but a generalized, infection. Of recent years the enthusiasm for cauterization has been revived in some quarters.

The treatment of the chancre consists, as a rule, in doing nothing. This is particularly important if there is any doubt about the diagnosis; for cauterization of the sore will destroy its normal appearance, prevent its normal evolution, and thus make the diagnosis further impossible before appearance of constitutional symptoms. In these cases simple cleanliness and dusting with calomel powder suffice. When the diagnosis of the sore is quite certain, excision may be practised to get rid of a none too pleasant lesion and to ease the patient's mind. No other results should be expected of it, although it is still within the realms of possibility that it may do good. Now that Schaudinn's discovery has made early diagnosis of the sore possible, the whole subject needs further experimental study. Extensive cauterization cannot be too heartily condemned; tampering with powerful caustics may turn relatively benign chancres into deforming phagedenic lesions which promptly heal when kept clean and let alone.

(b) When should constitutional treatment be begun? Briefly, it should be begun the moment a positive diagnosis of syphilis can be made. The disease should be attacked too soon rather than too late; for when treated from its commencement it generally shows itself amenable to treatment, benign in its symptoms, and relatively less severe as regards later manifestations. The increasing difficulty of an absolute cure, as time advances after infection, has been abundantly proved by recent serological studies. On the whole, syphilis is more dangerous and less curable when treatment is begun late; early treatment often prevents many of the distressing and compromising secondary symptoms, and, if the diagnosis be made, "it is impossible," in the words of Hutchinson, "to commence too soon." But *only if the diagnosis be made*; for in cases where careful and minute examination of the lesion leaves one in doubt as to its nature it is better to wait until the appearance of confirmatory evidence before prescribing mercury. Previous to the work of Schaudinn and Wassermann a large proportion of the cases fell in the doubtful class. Physicians frequently found themselves compelled to waste precious time waiting for the evolution of symptoms sufficiently characteristic to warrant instituting the tedious and disagreeable treatment, which could not be undertaken and efficiently carried out if there was any doubt that the disease really was syphilis. At present, however, the nature of the initial lesion can be positively recognized in a large number of cases by finding the *Treponema pallidum*, and in the later stages a positive Wassermann reaction will give us the necessary information. In a large number of cases treatment therefore may be begun as soon as the patient is seen.

1. *Auxiliary Treatment.*—(a) *Diet.*—Many idle words have been written as to diet; and although the matter is by no means unimportant, it is quite simple and to be summed up in a few words. The keynote is the avoidance of excess. Irregularities of diet are to be forbidden and

food and drink which cause diarrhoea or are prejudicial to the gastrointestinal functions are to be avoided. Alcoholic excess is particularly dangerous. With these exceptions the diet should be interfered with as little as possible.

(b) *Hygiene*.—Here again avoidance of excess is the keynote. Overstimulation of an organ directs the syphilitic virus to that organ. Cerebral syphilis, for example, is especially common after nervous and intellectual overwork, after excitement, dissipation, and venereal or other excesses. Again, buccal syphilides are most frequent and most serious in tobacco users. For these reasons one should insist on the very great danger of overstrain to a syphilitic under treatment, and forbid tobacco.

Not an unimportant part of the physician's hygienic duty to his patient consists in attention to his state of mind. "Avoid sad passions" was the old advice to syphilitics; but, as Diday said, "Of all the anguishes, it is often the syphilitic anguish which lies heaviest on the syphilitic." This is the sad passion which the physician should correct. He can, fortunately, tell his patient, with truth, that the disease is curable, that safe marriage is possible, and that the prospect for healthy posterity is good. This wholly warranted assurance may be a very vital part of the treatment.

(c) Special attention must be paid to patients with *nervous predispositions*. It is the nervous system which is most often attacked by tertiary syphilis, and to these dangers nervous patients are more liable than others. It is the hereditarily neuropathic patients and the patients subject to nervous overwork who are especially subject to these calamities. Neurasthenia may be called one of the "localizing causes" of syphilis, and neurasthenic patients should be particularly careful in the avoidance of excess of every kind. Hydrotherapy and other more specifically neurasthenic treatment should also be used.

2. *Specific Treatment*.—Syphilis is one of the few infectious diseases for which therapeutic specifics are known; and in this instance there are four of them: mercury, potassium iodide, salvarsan, and neosalvarsan.

(a) *Mercury*.—This drug possesses a power over syphilis, at least in its secondary stage, that has few parallels in medicine. This power is in direct proportion to the amount of the drug taken up by the economy. The drug is, at the same time, not without its injurious effects, and cannot be recklessly given. In the effort to combine the maximum of therapeutic effect with the minimum of untoward symptoms, several methods of administration have come into use.

(1) *Ingestion*.—This is the method most widely used, not because it is free from disadvantages, but because it is practical, in the sense that it is easy, convenient, and efficient. Nearly all the preparations of mercury known to chemistry have been administered by the mouth, but it is the proto-iodide and the bichloride which have, after long experience, proved themselves most valuable. Proto-iodide is insoluble and can therefore only be administered in the form of pills. The dose varies from gr. $\frac{1}{6}$ to gr. j (0.01 to 0.06 gm.). A small dose of opium, gr. $\frac{1}{3}$ (gm. 0.02) is often prescribed with the mercury to prevent gastric

irritation, the most famous combination of this sort being Ricord's pill.¹

Bichloride of mercury may be given either in pills or in solution. The usual dose for an adult is gr. $\frac{1}{16}$ (gm. 0.004) three times a day. This, too, is often combined with opium, to assure gastric tolerance, but the drug is preferably given without opium in pill form or in solution with a small amount of gum acacia. Sublimate solution is irritating to the stomach and should be given in a dilute form. On account of its objectionable taste and also to diminish gastric symptoms, syrup of sarsaparilla or peppermint may be prescribed with it. If taken in milk the drug is better tolerated by the stomach.

Gray powder (mercury with chalk) is a form of mercury particularly lauded by certain authors. It may be given in gr. $\frac{1}{2}$ (0.03 gm.) doses, and was Hutchinson's favorite form of treatment. In cases of visceral disease with ascites the well-known Guy's or Addison's pill (containing calomel, digitalis, and squill) is useful; but in general the visceral lesions (more particularly syphilitic hepatitis) require in addition the administration of iodides. Bichloride of mercury is also frequently prescribed in combination with potassium iodide.

The mercurials administered by the mouth may also be given per rectum in the form of suppositories. This is mentioned for the sake of completeness, rather than because it possesses any advantages.

(2) *Inunction*.—This is the oldest of all the methods of administration of mercury. It consists in anointing the skin with salves containing the drug in a suitable form and in the olden days included, among other things, as an important part of the treatment, depuration by purgatives and by bleeding. The ointment most often used is the well-known blue ointment, composed of equal parts of mercury and lard (double mercurial ointment, Neapolitan ointment). Lanolin may be substituted for the lard and is said to penetrate the skin better. Mercurial soaps have also been used, but, in spite of certain advantages, have not replaced the blue ointment. Mercury-vasogen (which may be had in 33 per cent., 50 per cent., and 75 per cent. mixtures, and should be ordered put up in gelatin capsules containing the required dose) is a very clean and efficient form of ointment for this purpose. Its expense is its only disadvantage. The average dose of mercurial ointment is 1 dram. For women, who are more subject to salivation from inunctions than men, $\frac{1}{2}$ dram is, as a rule, a sufficient dose. Infants tolerate inunctions well and proportionally larger doses may be prescribed for them; in quite young infants 15 to 30 grains may be safely used. The inunctions should be carried out to the point of dryness; for a dose of 1 dram this requires at least 30 minutes. One inunction is usually prescribed per day for six days of the week; it is omitted on the seventh day, when a hot bath,

¹ The original formula of Ricord was as follows:

Proto-iodide of mercury	3 grams
Extract of thebain	1 gram
Thridace	3 grams
Confection of roses	6 grams

For sixty pills

preferably a Turkish bath, or a sweat bath is taken. The hairy regions of the body should be avoided, as inunctions in these regions lead frequently and rapidly to stomatitis and often cause dermatitis. To avoid mechanical irritation, the seat of the inunctions should be varied, the sides of the thorax and the inner surfaces of the thighs and arms being chosen.

The inunctions are best given at night before retiring, the site of the application being covered with cotton, after rubbing, to prevent soiling and to keep the ointment from being wiped away. The inunction treatment is quite efficacious even when simply carried out; but a regular sweating bath is beyond doubt of advantage, and life at a mineral spring, where hydrotherapy is assiduously practised, large amounts of water drunk, and frequent Turkish baths taken, make it possible for the patient to absorb larger amounts of mercury than can be taken up without such auxiliary treatment. The inunction treatment should be interrupted from time to time and a recess of a few days taken to avoid stomatitis, and the mouth, in all cases, should be very carefully watched during the treatment.

(3) *Injection*.—The introduction of mercurials under the skin was originated by Hebra and Hunter, but it was first widely used after the publications of Lewin in 1867. The injections are best made into the buttocks, well above the ischial tuberosities, the two buttocks being used for alternating doses. An all-glass syringe is the best to use; the needle should be of sufficiently large calibre, and it is essential that it should be long enough to reach well through the skin and subcutaneous fat. For the injections, although often spoken of as hypodermic, are, or should be, intramuscular. The skin is washed with green soap and water and swabbed with ether. The needle is then plunged straight into the muscle, and watched for a moment to see that no blood escapes. If blood *does* escape, the needle should be reinserted. The syringe is then attached and the injection made. When the needle is withdrawn, a small collodion and cotton dressing over the puncture wound is sufficient.

Both soluble and insoluble forms of mercury have been used for this purpose. Of the former, bichloride and biniodide; of the latter, metallic mercury, calomel, and salicylate of mercury have been the ones most frequently employed. The following are the formulæ:

Bichloride.—

Hydrarg. chlor. corros.	gr. j
Glycerini	5ij
Aquæ destillat.	5ij

Sig.—Injections of $\mathfrak{m}\mathfrak{v}$ to \mathfrak{xv} every one, two, or three days.

Biniodide.—This may be given in a 0.4 per cent. solution in olive oil. The injections may be given every day, the dose at the start being $\mathfrak{m}\mathfrak{x}$, which is rapidly increased to $\mathfrak{m}\mathfrak{xxx}$ or $\mathfrak{m}\mathfrak{l}$.

Metallic Mercury.—This is given as the gray oil, introduced by Lang, of Vienna. Half an ounce of mercury is rubbed up with 2 ounces of anhydrous lanolin, and the mixture then increased to 5 ounces by the addition of paraffin oil. Enough carbolic acid should then be added to

make a 2 per cent. solution for antiseptic purposes.¹ This mixture should not be warmed, in which case the mercury separates out; nor cooled, in which case the solution stiffens. The dose is $\mathfrak{m}\text{x}$ and the injections may be given once a week or once every five days.

Calomel.—This is given in glycerin, according to the following formula:

Calomel	gr. xxiv
Glycerin	$\overline{5}\mathfrak{j}$
Distilled water	$\overline{5}\mathfrak{j}$

This may be sterilized by placing the bottle in which it is kept in boiling water and keeping it there for an hour. The dose is $\mathfrak{m}\text{v}$ to $\mathfrak{m}\text{xv}$ (gr. $\frac{1}{2}$ to $1\frac{1}{2}$) injected every five to fifteen days. Olive oil, oil of vaselin, oil of almonds, and distilled water may also be used for making the suspension.

Salicylate of Mercury.—This is best given as a 10 per cent. solution in liquid albolene, which may be sterilized by heating. The dose is $\mathfrak{m}\text{x}$ once or twice a week. The injections usually cause no local disturbances, but indolent nodosities have been seen after the use of salicylate.

For the insoluble salts, 10 to 15 injections repeated at intervals of five to fifteen days constitute an ordinary course. The soluble salts must be administered more frequently; 20 to 30 injections, at intervals of two or three days, are regarded as a course. Two or three courses may be given during a year.

Certain authors have advised the use of massive doses of soluble salts of mercury. This is dangerous; for the rapid absorption, which is quite beyond one's control, may lead to alarming symptoms. Moreover, although intense mercurialization may be thus produced it does not appear that the influence of such injections on the disease is a persistent one.

Intravenous injection of mercurials, introduced by Bacelli, of Rome, has, in spite of its dangers, found certain staunch supporters. Bacelli used bichloride in 0.1 to 0.2 per cent. solutions, 1 cc. (representing gr. $\frac{1}{4}$ to gr. $\frac{3}{2}$) being injected. The therapeutic effects have not, however, been superior to those of other methods. Lang has suggested paravenous injections for the purpose of having the mercury reach the blood promptly, but not too directly.

(4) The introduction of mercury by fumigation, by mercurial baths, and by the application of mercurial plasters should be mentioned for completeness, though the methods have little more than historical interest.

Merits of the Various Methods of Mercurial Administration.—Ingestion is particularly appealing by reason of its simplicity. It is less liable than inunction to cause stomatitis, and the stomatitis which it causes is of a less rapid and severe type. It avoids the pain and occasional accidents of injection. The method is, on the average, best suited to the occupations, convenience, and social and professional obligations of the average patient; and the probability that convenience of form of

¹ This is the principle, although not the exact formula, of Lang. The formula is the one recommended by Lambkin, of the British Army.

treatment will make for prolonged and efficient treatment is not to be lost sight of. Patients who will not submit to inunctions or return for injections will swallow pills almost indefinitely. On the other hand cases which do not yield to ingestion sometimes clear up promptly when intramuscular injections are used. It must not be forgotten that the method of ingestion has the disadvantage of leaving the treatment largely in the hands of the patient. It is contraindicated when the digestion is poor, or when experience shows the stomach to be intolerant to the drug; when the patient is cachectic and must have his digestive powers respected; when the digestive organs must be left free for other remedies which may be required; and when a pressing and urgent danger renders rapid mercurialization necessary.

The chief advantage of *inunction* is its active therapeutic effect. This may be an absolute indication for the choice of this method where urgent symptoms are present. But the absence of gastric complications is an additional advantage. Again, inunction leaves the stomach free for other medication; either the exhibition of iodides, when mixed treatment is carried out, or the administration of auxiliary medication (potassium bromide, tonics, etc.). On the other hand, it is a dirty, inconvenient, and repulsive method, involves a certain amount of publicity, and often discourages patients, leading them to abandon treatment altogether. It is occasionally accompanied by diarrhœa and by dermatitis; and quite commonly by stomatitis which occurs more frequently with this method than with any other. Moreover, the stomatitis which it causes is more rapid in its onset, more general and more intense in its manifestations than that seen after ingestion. Inunctions are also somewhat uncertain in their effects; one patient responds well to them, another badly. This is no doubt due to the way in which the rubbing is done, and for this reason the method is not always applicable. It cannot be too strongly insisted that patients who are receiving inunctions should be carefully watched, particularly as to the development of stomatitis; and that care should be taken that the rubbing is well done. The method is indicated in severe cases (cerebral and spinal syphilis), in cases refractory to other methods, in dyspeptics and those subject to diarrhœa, and in cachectic patients. It is of particular value in the treatment of syphilis in young infants, whose lives may depend on the integrity of the digestive system.

The method of *intramuscular injection* is a relatively accurate one. The drug must be administered by the physician, and deceit as to the amount of the drug taken is avoided. The chief advantage of the method is its therapeutic intensity; it induces mercurialization rapidly and intensely, and is of particular value in the presence of urgent symptoms. It also leaves the stomach free for other medication, and does not, as a rule, cause intestinal symptoms. It is claimed that the hypodermic method ensures the most exact dosage of mercury; but this accuracy is an apparent rather than a real one; for the sufficient dose of a drug is to be estimated not alone by the amount given, but by the physiological effects obtained, and these can be estimated quite as well when inunctions or ingestion are used. Pain and local irritation are strong

objections; for, aside from the inconvenience caused, these are often sufficient to drive the patients away and make them neglect treatment altogether. The formation of nodosities and sloughs is occasionally seen, although only occasionally with present-day technique. The method, not without its disadvantages, is strongly recommended by many competent men. It is not wholly free from danger. Several cases of pulmonary embolism have been reported following the subcutaneous injection of calomel; and hemorrhage and nervous accidents (partial paralysis, trophic disorders, etc.), although rare, have occurred.

Intravenous injections may be given quite without pain. Local accidents are, as a rule, absent: the dose given is mathematically controlled; and much has been claimed, by enthusiasts, for the therapeutic results. As a rule, however, it has been generally abandoned, and is now recommended only when very rapid action is required. The technique is not altogether simple, as the vein may be missed; and local accidents, although not frequent, do occur. Moreover, the therapeutic effects of the method have not been encouraging, and most authorities hesitate to advise such sudden introduction of a toxic substance directly into the blood-stream.

The Disadvantages of Mercury.—Aside from the question of method of administration, the dangers of the drug itself must be considered. *Stomatitis* is the complication most frequently seen. This was formerly regarded as an essential part of the cure; in the days of Astruc "a good cure required a good salivation of 4 or 5 pounds a day." The stomatitis now observed, however, is usually of a milder type and begins as a gingivitis. The saliva becomes stringy and superabundant; there is a metallic taste in the mouth; the gums (especially of the lower jaw) become reddened and swollen and bleed easily; the teeth become tender and appear to the patient to be elongated. There is a metallic and fetid odor to the breath. In bad cases, now not often seen, the entire mucous membrane of the mouth is swollen, ulcerated, and bleeding;ropy saliva wells from the lips; the teeth are exceedingly tender, become loose, and may even fall out. The ulcerations of the buccal mucosa may resemble mucous patches quite closely. Stomatitis may often be prevented by prophylactic measures, including: (a) Choice of remedy and method of administration; ingestion is less frequently accompanied by stomatitis than injection or inunction, and proto-iodide more frequently than sublimate. (b) Hygiene of the mouth. Neglected mouths are particularly subject to stomatitis, and mercury should never be given without inspection of the mouth. Where this is in bad condition, attention should be paid to it. But in any case the teeth should be carefully and regularly brushed and the mouth frequently washed with a solution of chlorate of potash or some astringent wash. The gums may be occasionally painted with tincture of iodine. Patients should also be informed of the buccal accidents of mercury and told to report immediately if any symptoms are noticed. On the least sign of buccal irritation, mercurial treatment should be discontinued.

Salivation, when present, is treated, as follows: Stop mercurial treatment and order immediate and repeated Turkish or vapor baths. See

that the bowels are kept open and that large amounts of water are taken. Order a potassium chlorate or potassium permanganate mouth wash to be used every hour, and internal doses of potassium chlorate (5 grains three times a day) for three or four days. Atropine in doses of gr. $\frac{1}{100}$ (0.00065 gm.) may be given. The gums may be painted with the following solution:

Tinct. kramerie.	
Tinct. iodi	āā 5v
Tinct. myrrh.	5ijss

In ulcerous stomatitis, hydrobromic acid or silver nitrate should be used to cauterize the ulcers.

Gastro-intestinal complications are not infrequent during mercurial treatment. These may take the form of pains in the stomach, colic, diarrhoea, loss of appetite, or even persisting dyspepsia. Some corrective (such as opium) will often suffice to prevent or attenuate these complications. But even the strongest stomach may become fatigued by the remedy, and treatment should therefore be now and then suspended, to give the digestion a respite.

Disturbances of nutrition, in the form of languor, anemia, want of appetite, fatigue, and emaciation, occasionally occur, particularly when mercury has been too strenuously prescribed. The nutritional dangers of mercury have, however, been exaggerated; their occasional occurrence is but one more argument for careful and intermittent administration.

Cutaneous Complications.—Irritative dermatitis from inunctions is a local affair and may, by varying the site of inunction, be avoided. The absorption of mercury also causes eruptions. They are due to a personal idiosyncrasy and occur with even very small doses. The most common form is that of desquamative polymorphous erythema. In the milder cases, the symptoms consist only in local heat and itching, with slight fever. Occasional cases are severe, the clinical picture being that of a severe, extensive burn.

Other manifestations of hydrargyrosis are albuminuria, cylindruria, and changes in the nervous system (particularly polyneuritis).

(b) *Potassium Iodide.* This drug takes the place in the therapeutics of the tertiary stage which mercury holds in that of the secondary. It is very soluble in water, rapidly absorbed, and appears in the urine twenty minutes after ingestion. The economy soon becomes impregnated by it and it may be found in all the secretions. Its antisymphilitic power is miraculous and its power to dissolve luetic tumors is one of the most dramatic things in therapeutics. The drug may be administered by the mouth, by the rectum, or hypodermically; but inasmuch as it is usually well tolerated by the stomach, the second two methods have little more than theoretical interest. In certain rare cases the administration by enemata might be indicated, as in unconscious patients in whom it was not desirable to pass a stomach-tube; but for all practical purposes the drug should always be administered by the mouth. It should be given in weak solution, as strong solutions have a disagreeable taste and irritate the stomach. The taste may be masked by giving the drug in milk

or wine or by adding peppermint or one of the syrups (the best is syrup of bitter orange). When the taste of iodide is persistently nauseating, one has to experiment until some pleasant drink is found which successfully masks it. The drug should be taken after or during meals. In some patients it causes constipation, in others diarrhœa; and a mild purgative or astringent should in these cases be prescribed with it. It may be ordered in the saturated solution, the required number of drops being put into the milk or other drink which is to be used.

As to the dosage, there is divergence of opinion. Some advocate small, others extremely large, doses. Fournier thinks that the method of beginning with small doses is bad, for it is the small doses which appear to be particularly harmful. On the other hand, he is strongly against what he calls "iodide debauches." He begins, for an adult man, with 30 grains daily (given in three doses); for a woman, with 15 to 20 grains. The dose is gradually increased until it reaches 45 to 60 grains daily, and here it remains. When the indications are very urgent larger doses (beginning with 70 to 90 grains and rapidly increasing to 150 to 180) are given; but doses of 500 grains he considers useless "intemperance." When tolerance for the drug is established, the curative value apparently diminishes, and the dose must therefore be increased. Other authors, however, advise larger doses, beginning with 30 to 40 grains daily and increasing a grain a day until about 250 grains daily are given. Gottheil reports a case of gumma of the meninges which only showed improvement when 900 grains were administered daily; half of this was introduced into the stomach through a tube and the rest into the rectum in enemata. Whether parasyphilitic affections would be prevented by routine employment of massive doses, as claimed by some authors, is a point still unsettled.

Iodide of sodium, ammonium, and rubidium, iodine, iodoform, and other iodine compounds have been used instead of iodide of potassium; but none of these has yet proved itself a satisfactory substitute.

Iodism.—Potassium iodide, like mercury, joins with its therapeutic value certain untoward effects. The occurrence of these symptoms seems to be determined by an idiosyncrasy of the patient. They appear after small doses and often early in the treatment. The most common are the iodic taste, coryza, and acne. The taste is a slightly salty or metallic one, is especially noticed in the morning, and is most frequent in women. The coryza is much like that of an ordinary cold in the head; it is characterized by snuffing, a sense of nasal obstruction, running from the nose, frontal headache, etc. The discharge from the nose is usually serous. The coryza may disappear in a few hours or last, in a subacute stage, throughout the treatment. The acne eruption generally appears on the face in the form of recurring crops of acneform pustules, seldom more than four or five at a time. Both the coryza and the acne may appear in severe form, the former resembling influenza (iodic grippe) and the latter appearing as a large, furunculoid, deforming eruption. Other rarer symptoms of iodism are neuralgic pains, especially of the jaws, and most often seen in women; a mild sialorrhœa, never so intense as in mercurial salivation; conjunctivitis; iodic purpura; gastro-intestinal symptoms

(nausea, vomiting, diarrhoea); swelling of the salivary and parotid glands (iodic mumps); and localized œdema, especially of the eyelids.

The eruptions of iodism, which are sometimes severe and occasionally fatal, appear in three general types: the bullous type (iodic pemphigus), the furunculocarbuncular type, and the pustulocrustaceous type. The latter may be impossible to distinguish from tertiary syphilides; the rapidity of invasion, the initial form of the eruption, the inflammatory character of the areola, the soft base, and the disappearance of the eruption on suppression of the drug make the diagnosis. Purpura may occur. Iodic œdema of the respiratory passages, sometimes requiring tracheotomy and occasionally ending in death, is another rare symptom of iodism which must be mentioned.

The accidents of iodism are not as a rule severe; the symptoms often disappear as tolerance is established, and suppression of the drug is not necessary. When they do not disappear, it may be discontinued for a short period. For patients who are subject to localized œdema and to prevent the nasopharyngeal accidents, belladonna may be exhibited, 1 grain of the extract being given daily.

Mixed Treatment. It is true that mercury is the drug, *par excellence*, which is indicated, roughly, in the early stages of syphilis; and that the iodides produce their most remarkable effects in the later stages of the disease. Syphilis, however, may be entirely cured without the use of iodides, the administration of which in lues is only a matter of relatively recent years. Furthermore, iodides have, as a rule, only a slight influence on most of the secondary phenomena. They are not, therefore, in any sense of the word a substitute for mercury. To say these things is by no means to warrant us in dividing syphilis into two halves, for one of which mercury and for the other iodide is indicated; for iodide may be of use in the secondary stage and mercury is an antisiphilitic at every period of the disease.

In the secondary period iodide has a marked influence on the headaches and should be prescribed in 15 grain (1 gm.) daily doses. It is also of value for the vague neuralgic pains which are especially common in women. In early malignant syphilis—which is really tertiary syphilis succeeding the chancre without a secondary stage—iodides are of benefit; and they are indicated whenever mercury cannot be tolerated by the patient in any form. Mercury, on the other hand, seems to be always useful as an auxiliary agent in the tertiary stage; it may, indeed, even replace iodides, certain of the lesions (notably sarcocœle), which had failed to yield to iodides, having been cured by mercury. Moreover, it must be remembered that it is mercury which cures syphilis; iodide “erases the symptoms.” “As a preventive medication,” therefore, “there is much more confidence to be placed in mercury than in iodide.”

For these reasons the method of mixed treatment is the one that should be followed. The drugs may be administered separately or together. The best plan is to order a solution of iodide in syrup to be taken at the same time as the mercury; or to prescribe mercury by inunctions and potassium iodide by the mouth. A very satisfactory plan is to combine the exhibition of potassium iodide with mercurial injections.

(c) *Salvarsan*.—This remarkable synthetic arsenic compound was first produced by Ehrlich and shown to possess a specific toxicity for *Treponema pallidum* and other parasites, while almost without toxicity for the animal body. The chemical name of the preparation is dioxy-diamido-arsenobenzol, and it is used in the form of the hydrochloride of the sodium salt. Its value for syphilis was first shown by the experimental demonstration that its injection into a syphilized rabbit caused complete disappearance of the *Treponema pallidum*. Clinical application of these findings was then made, every possible precaution having been taken, and the drug having first been tested on two of Professor Alt's assistants, who volunteered for the purpose. The results of these extensive clinical studies by Wechsellmann and many others have demonstrated that salvarsan, when used with proper precautions, is a drug of the greatest value in the treatment of syphilis. The specific power of the substance depends on the anchorage of the trivalent arsenic by chemoceptors of the parasites; this anchorage does not occur with preparations in which the arsenic group is completely satisfied. The hope of Ehrlich that this drug would effect a complete cure of syphilis by the total destruction of all spirochetes has not been fulfilled. It has proved to be extremely valuable as an abortive measure in the early stages of the disease.

The drug is a highly powerful one; and during the early days of its use, in spite of the great care taken, a number of accidents occurred. There were a few deaths following injection; these have been subjected to very rigid scrutiny and it seems altogether likely that all of them were due to faulty technique, particularly to ignorance as to the contra-indications.

The almost constant occurrence of a chill and other untoward symptoms which followed the injection of salvarsan in its early days have now been practically eliminated by the observation that these phenomena either do not occur, or occur in very slight degree if *freshly distilled* water be used to dissolve the drug. Moreover, it has been shown that the newer preparation (neosalvarsan) is without these disadvantageous properties of salvarsan itself, and injections may therefore now be made without any inconvenience to the patient whatever.

These arsenic preparations should not, however, be indiscriminately employed; and it is probably best to preface the description of their use with a statement of the contra-indications.

1. The injection of the new arsenic preparations affects the blood-pressure and causes reactionary inflammation in the luetic lesions. They should therefore be used only with the greatest care in myocarditis, endocarditis, coronary disease, aneurism, and cerebral endarteritis.

2. Arsenic may cause hemorrhage, and these drugs should therefore never be used after fresh operations, in phthisis with cavities and in hemiplegia in the young.

3. If albuminuria is present it is probably wiser to use mercury until the albumin disappears, but there is not general agreement on this point.

4. The arsenic preparations should not be use in diabetics.

5. These drugs must be used cautiously in the presence of intracranial lesions.

6. Old age and young infancy are relative contra-indications.

7. The most important contra-indications are the late nervous lesions. These include particularly: (a) Lesions of the optic nerve; (b) late cases of tabes dorsalis, especially if the Wassermann reaction is negative; (c) general paralysis of the insane; (d) acute cases of cerebrospinal lues; (e) nervous lesions in congenital lues.

This list is probably unduly full; a number of these contra-indications would not be recognized by competent observers; but on the last group (nervous lesions) all would lay stress.

Technique. The drug is now frequently used in its latest form, a derivative of the original salvarsan known as neosalvarsan (dioxy-diamido-arseno-benzene-mono-methane-sulphinate of sodium). This is a yellowish powder of peculiar odor which dissolves readily in water, with a completely neutral reaction. The average single dose for men is 0.6 to 0.9 gm., for women 0.45 to 0.75 gm.; for men not more than 1.5 gm. and for women not more than 1.2 gm. should be given at a single dose. The drug may be given intravenously or intramuscularly, but never subcutaneously. The powder should be dissolved in freshly distilled and sterilized water, at room temperature (never above 20° to 22° C). For intravenous injection 25 cc. of water are required for each 0.15 gm. of neosalvarsan. For intramuscular injections approximately a 5 per cent. solution should be used, the injection being preceded by local anesthesia with novocain. Solutions of neosalvarsan oxidize very readily and the solution must therefore be prepared fresh and used promptly. When given intravenously, the injection of the drug should be preceded and followed by the injection of a small amount of salt solution, and this can readily be accomplished by using a two-bottle apparatus.

For salvarsan a similar technique is employed. The dose is different, 1.5 gm. of neosalvarsan corresponding to 1 gm. of salvarsan. In America there is a growing feeling that neosalvarsan, though undoubtedly less liable to cause disagreeable symptoms, is less efficient than salvarsan. Some advise using neosalvarsan for the early injections and replacing it by salvarsan after the patient's tolerance for arsenic has been demonstrated.

The earlier the arsenic preparations are administered, the better the chance of cure. In the primary stage of the disease an injection should be given immediately the diagnosis is made. In the secondary stage three or four injections should be given under the control of repeated Wassermann reactions. Probably the most brilliant results are seen in the cutaneous gummata of the tertiary stage. Fitz has reported good results from the local application of a 10 per cent. saline solution of salvarsan to the mouth lesions and the ulcerations of syphilis.

In syphilis of the central nervous system, treatment with salvarsan should not be adopted in the acute stage, and in no nervous disease should more than a half dose be used. The aim should be, by repeated small doses, to convert a positive Wassermann reaction into a negative. The results in the treatment of tabes have not been satisfactory. Many observers advise against its use in this condition; but Wechselmann favors it on account of the relief of symptoms, even when the Wassermann

reaction is negative. Recently, Cole has advocated injecting salvarsan into the vein, in cases of tabes; and then withdrawing blood, separating the serum and injecting this into the subdural space. The purpose is to obtain the good effects of the drug without the dangerous toxic action which it exhibits when injected as such into the spinal canal. The results have been suggestive.

It should not be forgotten, in our enthusiasm over salvarsan, that mercury and potassium iodide are wonderfully efficient drugs in the treatment of syphilis; nor should salvarsan be regarded as a panacea which will "cure in one injection." As a triumph of experimental therapeutics the synthetic arsenic compounds are without peers; they offer a simple and effective method of controlling symptoms, and of assisting in the cure of the disease; in the rare cases which resist mercury they may accomplish wonders. But it seems probable that in all cases the injections of salvarsan or neosalvarsan should be supplemented by a thorough course of mercury.

Local Manifestations.—1. *The Syphiloderms.*—These, as a rule, require no attention. When on the face or hands they may be made to disappear more rapidly by the use of white precipitate ointment. The tuberculous and pustular syphilides require more energetic treatment; white precipitate ointment may be used, or a 10 to 20 per cent. solution of the oleate of mercury in oleic acid. For the alopecia, local inunctions of blue ointment are advised.

2. *Mucous Patches.*—Cleanliness is very essential, and a mouth wash of bichloride (1 grain to 6 ounces of water) should be prescribed. The use of tobacco should be forbidden. The individual lesions should be touched occasionally with the nitrate of silver stick.

3. *Condylomata* and *moist papules* are, as a rule, best treated by cleanliness and the use of a bland dusting powder. Large growths may be cauterized with silver nitrate. Condylomata may also be excised if they present a suitable pedicle. Simple clipping with the scissors usually suffices; the hemorrhage is slight, a small dressing is all that is needed, and the wound heals well.

4. *The Eye.*—When syphilitic iritis is present, it is necessary to administer constitutional treatment in the most energetic manner possible—best by injection. In addition, the pupil should be kept dilated by atropine.

The General Management.—The patient is generally first seen after the appearance of a suspicious genital sore; and the physician's first duty is to use every possible means, microscopic examination for Schaudinn's organism being one of them, to make a positive diagnosis. If this cannot be made, no treatment should be used; the patient should return for frequent examination so that the evolution of the sore may be followed and constitutional phenomena seen as early as possible. The moment the diagnosis is made, treatment should be instituted. The purpose of this treatment is to bring the patient as rapidly as possible under the influence of the largest possible dose of either the mercurial or the arsenic preparations. Four or five intravenous injections of salvarsan or neosalvarsan, at intervals of five to seven days, followed by a course

of insoluble mercury intramuscularly makes such an intensive form of treatment possible without the dangers of intoxication from either drug. This *principle of intensive treatment*, in which salvarsan or neosalvarsan is used to control the early symptoms, but is itself fortified by vigorous mercurial treatment, must control the management of a case of syphilis if the disease is really to be cured. Nor must it be forgotten how successful such treatment is, for if the number of recurrences after salvarsan alone is discouraging, one must remember that the standard by which we judge the effect of treatment has risen greatly since the introduction of the Wassermann reaction; and that the control of the treatment of the disease even by this rigid test makes it clear that syphilis can, in many cases, be completely eradicated if the specifics be exhibited early and with vigor.

There is not general agreement as to just how the arsenic preparations and mercury should be combined. Both salvarsan and neosalvarsan are expensive; and in many dispensaries only one injection is possible, the chief reliance being placed, as formerly, on mercury. The ideal, however, should be to use frequent injections of the arsenic preparations: and then to keep the patient under a moderate mercurial treatment.

When, for any reason, mercury alone is used one may begin with proto-iodide pills, gr. $\frac{1}{4}$, three times a day. This is, however, a *small dose*, and must be increased very soon until the patient is receiving at least $1\frac{1}{2}$ to 2 grains a day. The usual error is to prescribe proto-iodide in too small rather than too large amounts. Inunctions may also be ordered, particularly if compromising lesions are present on the face. The patient should be carefully watched at first in order to determine how the mercury is being borne, and the dose should, if possible, be pushed to the point of toleration. This will require experimentation. If the method of ingestion is badly borne, injections may be tried; some patients take one form well and others another, and the method of choice must depend on the reaction of the patient. The general health of the patient must be cared for, the mouth and teeth scrupulously watched. Regular Turkish baths should be ordered; and if the patient can afford it, frequent trips to mineral baths, both for change of scene and for specific therapeutic effect, may be of value. Early in the secondary stage iodides should be ordered in addition to the mercurial treatment. Often the case will run along smoothly, but many patients will tolerate mercury poorly or will neglect their treatment; and these cases will require all the therapeutic resources which have already been mentioned.

Whether mercurial treatment should be continuous or symptomatic is a point which has been disputed. Continuous treatment is the plan advocated by Hutchinson, Keyes, and others. The drug is pushed just short of salivation in order to determine the toxic dose; and then is continued at a slightly lessened dose until active symptoms subside. It is then given in smaller amounts (the so-called tonic dose) throughout the disease, the appearance of symptoms being the indication for increase of the dose. The patient is thus kept steadily under the influence of the drug until the end of the second year.

The most rational plan, as well as the one which has given the best

clinical results, both as regards the cure of secondary symptoms and the prevention of tertiarism, is the one advocated by Fournier. This is known as the method of chronic intermittent treatment. Syphilis is a specific infection continuously present, symptoms or no symptoms; but the stomach will not stand mercury indefinitely, and the body, before long, renders mercurial treatment less and less effective by establishing a tolerance to it. For these reasons prolonged treatment, combined with regular periods of rest, is the most rational plan to pursue. The syphilitic patient, when first seen, is put on vigorous mercurial treatment for about two months. If no symptoms are present a rest of about four weeks is then given, when treatment is resumed whether symptoms are present or not. The second course lasts about six weeks and is followed by a second rest of two months. Medication is then resumed for six weeks and again suspended for several months, this plan being followed for three years. In this way four mercurial courses are given during the first year, three in the second, and two or three in the third. When the iodides are begun they should also be given intermittently, each course lasting about five weeks and being followed by at least a month's rest. This program is not, of course, absolute; in most instances the courses of mercury should be longer and the rest shorter than here advised; the details must be modified for the contingencies of particular cases; but the principle of chronic, prolonged, intermittent treatment must be adhered to.

That the treatment should be prolonged is beyond all dispute; just how long it should be continued is matter for some disagreement. Of one thing there is no doubt: the closer acquaintance with the disease becomes, the more the time limit of treatment judged necessary for its cure is extended. Safety can best be assured by controlling the course of the disease by the Wassermann reaction, taken about twice a year. In this way recurrences can be promptly recognized and treated.

Congenital Syphilis.—The mercurialization of the mother during pregnancy has been dwelt upon; it remains to consider the treatment of the syphilitic infant. The child should, in the first place, be nursed by its mother whenever possible, both to avoid infecting other women and because the mortality among artificially fed luetic infants is enormous. The treatment of the mother, which is a fairly efficient treatment of the nursing infant, should be continued throughout lactation. If symptoms appear (coryza, marasmus, eruption) the child itself must be given mercury, which is best administered in inunctions. About 10 grains of the mercurial ointment (for an infant a few weeks old) are smeared daily on the abdomen, under the binder. It is absorbed rapidly. Gray powder may also be used in doses of $\frac{1}{2}$ to 2 grains (0.003 to 0.12 gm.) thrice daily, given with sugar of milk. Mercurial baths (10 to 30 grains of corrosive sublimate to an ordinary baby's tub of water) may be employed, the child being "soaked" for ten to twenty minutes every other day. The local lesions may be treated with mild ointments; blue ointment mixed with 8 parts of vaselin is appropriate. It is particularly important to keep the child under observation during dentition and puberty.

PART II

DISEASES CAUSED BY ANIMAL PARASITES

(EXCLUSIVE OF PROTOZOAN INFECTIONS)

BY CHARLES WARDELL STILES, PH.D., D.Sc.

GENERAL DISCUSSION

Nature and Kinds of Animal Parasites.—A parasite is any organism which lives in or upon any other organism, called the host, and generally belonging to a widely distinct species, at whose expense it derives its nourishment and habitation. Thus the prime ideas in parasitism are food and association.

1. **Food.**—No distinct line can be drawn between a parasite and a predaceous animal, although, as a rule, the parasite attacks organisms which are larger, stronger, and more intelligent than itself, and does not immediately kill and devour its host, while the predaceous animal attacks animals which are smaller, weaker, and less intelligent than itself, and it kills and devours its prey.

2. **Association.**—This may present an instance of (a) *Mutualism*, when the partnership results in benefit to both parties, as in the case of the sponge growing on the back of a crab, or in the case of some of the bacteria in the mouth; or (b) *Commensalism*, when the association results in a benefit to one party (the messmate), but neither benefit nor injury to the other (the host), as in the case of the non-pathogenic *Entamoeba coli* (not *E. histolytica*) in man; or (c) *True parasitism*, when the association results in a benefit to the parasite, but an injury to the host, as in the pathogenic *Entamoeba histolytica*, or trichinae, hookworms, or the tapeworms in man.

A parasite may visit its host only at intervals to take up temporary residence and to obtain food; such animals (mosquitoes, bed-bugs, etc.) are called *temporary* parasites. Others are more or less stationary with their hosts, and are therefore called *stationary* parasites; of these, we may have *periodical* parasites, which spend a given period of their life with their hosts (as bots under the skin, or *Strongyloides stercoralis* in the intestine of man), or we may have *permanent* parasites, such as trichinae, in which the entire life-cycle is parasitic. Some parasites, as the hookworm, require only one host to complete their life-cycle; others, such as the large tapeworms, require two hosts—an *intermediate*

host in which the larval stage lives, and a *definite* or *final host* which harbors the sexual stage. All cases thus far cited are examples of *simple* parasitism, but we may have parasites which are parasitic in or upon other parasites, a phenomenon known as *hyperparasitism*.

We may further have *ectoparasites* (as lice) which live upon animals, and *endoparasites* (as tapeworms) which live in animals. The term *entozoa* refers primarily to the *endoparasites*, and *helminthes* refer especially to the parasitic worms, while *helminthology* is that part of zoölogy which deals with worms, especially the parasitic forms, and *helminthiasis* denotes an infection with parasitic worms.

Chance parasites, or *pseudoparasites*, are animals which are usually free-living but are, by chance, living as parasites (as the vinegar eel in the human bladder, or parasitic animals which by chance are not in their normal host (as *Fasciola hepatica* in man). *Spurious parasites* are objects which are described as parasites or mistaken for such, but which in reality are creations of the imagination (*Furia infernalis*, *Vermis umbilicalis*), or half-digested food (*Diacanthos polycephalus*; *Striatula*; banana cells mistaken for tapeworm segments, etc.).

Frequency.¹—As a general rule, the smaller a parasite is, the more individuals there may be in a patient; compare, for instance, *Taenia saginata*, *Ascaris lumbricoides*, *Oxyuris vermicularis*, *Entamoeba coli*, *Labdia duodenalis*.

There is no species of animal, and no race or class of man known to be free from parasites. We may lay down certain general rules covering the frequency of infection: (1) Certain parasites are more common among people of careless personal habits than among those of more careful personal habits; thus, as a rule, dwarf tapeworms, eelworms, and pinworms are more common in children than in adults, and whipworms are said to be more common in negroes than in whites. (2) Certain parasites (eelworms) are said to be more common among people who drink unfiltered water than in those who have a filtered water-supply. The difference in frequency is influenced, however, by the disposal of feces by a better sewage system in cities than in villages. (3) Certain parasites (trichinae, pork tapeworms) are likely to be more common among people who eat raw or rare pork than among people who eat their pork well cooked. (4) Certain parasites (hydatids) are more common among people who (as in Iceland) keep large numbers of dogs and live more intimately with them, than among people who keep fewer dogs in proportion to the population. (5) In general, animal parasitism increases from temperate to tropical climates. (6) All intestinal and some hepatic parasites decrease hand-in-hand with the increase of care exercised in a proper system of latrines or sewers.

Age and Sex of Patient.—Some parasites (eelworms, pinworms) are more common among children, while other species (large tapeworms and hydatids) are more common among adults of from twenty to forty years of age; some parasites (large tapeworms, hydatids, head-lice) are

¹ See also, Stiles and Garrison, 1906 a, pp. 1 to 77, "A Statistical Study of the Prevalence of Intestinal Worms in Man." *Bulletin* 28, *Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington*.

more common among women than among men, while other species (lung-flukes, pubic lice) are more common among men.

Fertility of Parasites.—Most parasites are exceedingly fertile, some of them almost representing egg-machines. This fertility is:

1. A natural result of their environment, since they live in the midst of their food, which their hosts provide for them; hence energy which might otherwise be expended in seeking necessary food, may here be turned to growth and reproduction; thus it is estimated that the fat tapeworm (*Taenia saginata*) increases at the rate of thirteen segments per day, growing 3 cm. per day for the first month and averaging 14 cm. per day for the second month, and producing 150,000,000 eggs per year.

2. Subject to natural selection, for the life-cycles are often very complex, hence in such cases the chances that any one egg has of reaching sexual maturity are very small, so that individuals which are only slightly fertile would probably not be represented by many generations.

3. In accordance with the *general* biological law (not without exceptions) that the smaller an animal, the more fertile it is.

Resistance of Parasites.—Some parasites, especially in their egg and encysted stages, are exceedingly resistant to external influences: the Persian argas may live five years without food; *Cysticercus cellulosae* may live four weeks or so after its host is dead; trichinae may live for months after their host (hog) is slaughtered; eggs with thick shells (eelworms, whipworms, *Taenia*) are more resistant than eggs with thin shells (hookworms, pinworms, dwarf tapeworm).

Seasonal Periodicity.—Some parasites show a decided seasonal periodicity: hookworms have a better chance to develop in warm, moist months than in cold or hot dry seasons; and in general this obtains for worms which do not require an intermediate host. For certain worms (as trematodes) which do require an intermediate host (as snails) the seasonal periodicity depends upon the seasonal activity of this host, and this activity may depend upon various factors, such as moisture and warmth.

Heredity of Parasites.—From the strict embryological point of view, it would be impossible to fulfil the condition necessary to demonstrate the heredity of any infectious disease in man, and when we speak of the heredity of these maladies in the higher animals it should be recalled that we are using the term "heredity" rather loosely. No parasitic disease is known to be hereditary in man, though we know of several diseases in lower animals (as in insects and ticks) which are hereditary in a stricter sense of the term; namely, the sexual products are infected before fertilization occurs.

Influence of Parasites upon Their Hosts.—Views regarding the injurious effects of parasites have passed from extreme to extreme, some authors going so far as to attribute to some parasites injurious actions which they surely do not have, and others going so far in the opposite direction as to see in the parasites a supposed advantage or even a necessity to the host. Let us recall, however, that the injury done may vary with the species, size, location, and number of the para-

sites, and with the condition and age of the host. This injury may be accomplished in various ways: (1) Nourishment is taken which should go to the host; (2) blood is taken by the parasite as food; (3) mechanical pressure irritates or causes atrophy of organs or parts of organs; (4) natural channels may be obstructed; (5) the wandering of the parasite may cause irritation; (6) substances may be excreted which have a toxic influence, and which may change the natural condition of the body fluids (blood); (7) injury to the intestinal mucosa or to the skin may form points of entrance for bacterial and protozoan infections; (8) injury to the intestine (or certain other organs) may result in other secondary disturbance.

Such injury does not, as a rule, go on increasing indefinitely in any geometrical progression because of succeeding generations of parasites, for the general rule obtains (with a few exceptions, as in infections with certain protozoa and with the vinegar eel) that *for every adult animal parasite found in the human body a separate embryo or larva must enter*. Thus, hookworms do not multiply generation after generation in the intestine, but the eggs must leave the patient and the resulting larvæ reënter the body in order to become adult.

Generic and Specific Infections.—In the following discussion, reference will be repeatedly made to infections as being identical or distinct generically or specifically. These terms are used in their zoölogical sense, to express more accurately the relation which the diseases of man bear to those of animals. Thus it has been reported that *Taenia solium* occurs in both man and dog. If this statement were correct, the dog would be a very important factor, from a public health point of view, in spreading *T. solium* and cysticercosis. The reported presence of this parasite in dogs is, however, based upon an error of identification, for there is a tapeworm belonging to the genus *Taenia* that does occur in dogs but it belongs to a species (*T. hydatigena*) specifically distinct from, but quite closely (generically) related to, *T. solium*. Hence, man and dogs, in this instance, have infections which are *generically* identical, since both parasites belong to the same genus, but *specifically* distinct, since the two worms represent distinct species (*T. solium* and *T. hydatigena*). On the other hand there is a specifically identical tapeworm-infection (*Dipylidium caninum*) which is said to be common to dogs and cats and which occurs in man.

Diagnosis of Parasitic Diseases.—The general rule may be laid down that the best method of diagnosing most parasitic diseases is by a microscopic examination: examine *sputum* for suspected parasitic diseases of the lungs; *feces* for suspected parasitic infections of the intestine and liver; *urine* for suspected parasites of the kidney or bladder; *blood, feces, and urine*, for suspected parasitic diseases of the circulatory system; *blood and muscle* for suspected infections of the muscle; *blood* for suspected infections of the lymphatic system. In some cases a diagnosis may be made by a gross examination of the feces. In some parasitic diseases, diagnosis may be safely made upon symptoms, especially if the patient is within the infected area of a given malady. The technique of fecal examinations can best be given here.

In *gross* examinations of the stools (for pinworms or expelled hookworms, etc.), the feces should be shaken up well with warm water and allowed to settle; pour off any floating material and wash the stool in this manner several times; the worms will thus be concentrated.

For *microscopic* examination of feces, take a small portion of fecal matter on the end of a match or toothpick, using a separate one for each stool; smear this in a drop of water on a slide; cover with an ordinary cover-glass, avoiding unnecessary pressure, and examine ten such preparations.¹

For eggs with thick shells (whipworms, large tapeworms, flukes), use a strong illumination; for worms with thin shells (hookworms, pinworms, etc.), use a more moderate illumination; examine first with medium magnification (8 mm. or $\frac{1}{2}$ -inch focal length), later with higher power. Microscopic examinations for intestinal parasites are made free of charge by all Southern State Boards of Health in the United States.

To make permanent mounts of eggs, preserve the material in alcohol; then transfer to 95 parts alcohol plus 5 parts of glycerin; allow the alcohol to evaporate slowly, and when evaporated to glycerin, mount the material in glycerin-jelly.

Serodiagnosis, by the precipitin test or the fixation of the complement, is coming into use in several parasitic infections, especially hydatid disease.

Treatment.—The *general* rule may be laid down that for verminous infections of the brain, bones, muscles, eye, lungs, liver, kidneys, spleen, blood, and lymphatics, there is no satisfactory specific medicinal treatment, although some of these cases may be treated surgically. Intestinal, bladder, and some skin infections by parasites may be treated medicinally.

Prevention.—So far as most verminous parasites in temperate climates are concerned, ordinary habits of cleanliness; ordinary care in preparing food: ordinary methods of meat inspection; a proper disposal of alvine discharges—as in sewers, or properly constructed privies; and a recognition of the fact that the dog is not a human being, are in themselves sufficient to prevent serious trouble (in form of epidemics) from most parasites in Australia, Canada, England, and the United States. In warm countries protection against mosquitoes will reduce certain verminous affections (filariasis).

Personal Rules of Hygiene.—(1) The use of spring, boiled, or filtered water will tend to decrease certain protozoan, fluke, and roundworm infections; (2) proper care of meat (protection from flies) and thorough cooking will protect against certain dipterous larvæ, certain tapeworms, trichinosis, and certain protozoa; (3) avoidance of depraved tastes for insects will aid in protecting against certain tapeworms; (4) keeping the hands and nails clean, especially after handling dogs, will aid in protecting against a certain tapeworm and hydatid disease; (5) personal cleanliness after defecation will aid in protecting against auto-infection with pinworms and *Cysticercus cellulosæ*; (6) wearing shoes in infected areas will help to protect against hookworm infection and the burrowing flea.

¹ For a bulletin by Hall, giving a summary of different methods, apply to U. S. Bureau of Animal Industry.

Public Rules of Hygiene.—(1) If sewage is used for fertilizing, it is best to grow upon the land, so fertilized, only such vegetables as are subjected to cooking before eating; (2) properly dispose of all feces, especially in schools, asylums, hospitals; (3) interdict nuisances, especially in warmer climates, and upon plantations, in mines and in digging tunnels and canals; (4) meat inspection in the local slaughter houses (the federal inspection covers only the abattoirs engaging in interstate trade); (5) segregate local slaughter houses and place them under the supervision of a competent veterinarian, who might well be a member of the local board of health; (6) keep swine in a less swine-like manner—especially see that the privy is not near the pig-pen; (7) swine-offal and swill should be first cooked in case they are fed to hogs; (8) destroy all ownerless dogs, and keep dogs away from slaughter houses—the dog pound is an institution of practical hygienic importance.

CLASSIFICATION OF ANIMAL PARASITES

Contrary to early ideas, the parasites do not represent a group of animals closely related to each other systematically, but rather several diverse groups, more or less widely separated but with somewhat similar biological habits. For the details of classification the reader is referred to works on systematic zoölogy; for the purpose of this article, we may divide the animal parasites as follows:

1. Unicellular animals, as the parasites of malaria Protozoa.
- Pluricellular animals; metazoa 2
2. Body more or less flattened dorsoventrally 4
- Body ordinarily round in transverse section 3
3. Body never annulated; never provided with legs; no jaws present 5
- Body annulated, or at least provided with mouth parts; usually breathe through a tracheal system; adults with jointed legs 7
4. Intestine, but no anus, present; one or two suckers present; body not segmented; parasitic in liver, lungs, blood, intestine, occasionally elsewhere; flukes *Trematoda*, p. 225
- Intestine absent; two or four suckers on head; body of adults segmented; tissue usually contains calcareous corpuscles; adults (tapeworms) parasitic in intestine; larvæ (bladder worms) parasitic elsewhere *Cestoda*, p. 245
- Intestine and anus present; ventral sucker on posterior end; body annulated like an earthworm; parasitic in upper air-passages, or externally, leeches, bloodsuckers *Hirudineæ*, p. 316
5. Intestine absent; armed rostellum present; very rare in man, in intestine; thorn-headed worms *Acanthocephali*, p. 296
- Intestine present; no armed rostellum 6
6. Intestine rudimentary in adult; rare, accidental parasites in intestine of man; hair snakes or horse-hair worms *Gordiaceæ*, p. 296
- Intestine present; parasitic in intestine, muscles, lymphatics, etc., very common and important; roundworms *Nematoda*, p. 270
7. Six legs present in adult; wings present in most species; larva annulated much like an earthworm; breathe through trachea; adults ectoparasites; occasionally larva is parasitic under skin, or in wounds, or an accidental parasite in the intestine; insects *Insecta*, p. 324
- Eight legs present in adult, six legs in larva; head and abdomen coalesced; ectoparasites; some burrow under the skin or live in the hair follicles; acarines *Acarina*, p. 317
- Four claws around the mouth; larva encysted in various organs; adult occasionally parasitic in nasal passages; tongueworms *Linguatulidæ*, p. 323
- Numerous legs present; occasionally accidental parasites in nasal passage or intestine; thousand leggers *Myriapoda*, p. 324

Organ distribution of parasites, according to their more common habitat.

MORE OR LESS GENERAL.—Trematoda: *Paragonimus*, p. 226; *Schistosoma* eggs, p. 239. Cestode larvæ: *Taenia solium*, p. 263; *Echinococcus*, p. 264, *Sparganum*, p. 270. Arachnida: *Linguatula*, p. 323; *Porocephalus*, p. 324.

INTESTINAL TRACT.—Trematoda: *Fasciolopsis*, p. 237; *Echinostoma* (*Fascioletta*), p. 238; *Heterophyes*, p. 238; *Gastrodiscus*, p. 238; *Watsonius*, p. 239. *Schistosoma*, p. 239. Adult cestoda: *Taenia*, p. 247; *Hymenolepis*, p. 252; *Davainea*, p. 254; *Dipylidium*, p. 255; *Dibothriocephalus*, p. 255; *Diplogonoporus*, p. 258; *Braunia*, p. 258. Nematoda: *Ascaris*, p. 287; *Toxocara*, p. 288; *Toxascaris*, p. 288; *Belascaris*, 288; *Lagochilascaris*, p. 288; *Oxyuris*, p. 291; *Trichostrongylus*, p. 294; *Ancylostoma*, p. 274; *Necator*, p. 272; *Physaloptera*, p. 293; *Oesophagostomum*, p. 294; *Terndens*, p. 294; *Strongylus*, p. 294; *Haemonchus*, p. 294; *Rhabditis*, p. 295, 303; *Anguillulina*, p. 294; (*Filaria*), p. 316; *Strongyloides*, p. 285; *Trichuris*, p. 295; *Trichinella*, p. 297. Gordiacea, p. 296. Acanthocephali: *Gigantorhynchus*, p. 297. Insecta, p. 328.

LIVER.—Trematoda: *Fasciola*, p. 235; *Clonorchis*, p. 230; *Opisthorchis*, p. 233; *Dicrocoelium*, p. 234. Cestoda: *Echinococcus*, p. 264.

LUNGS.—Trematoda: *Paragonimus*, p. 226. Nematoda: *Melaststrongylus*, p. 302.

URO-GENITAL SYSTEM.—Trematoda: *Schistosoma*, p. 239. Nematoda: *Anguillula*, p. 315; *Agamomermis*, p. 316; *Leptodera*, p. 316; *Diectophyme*, p. 316.

LYMPHATIC SYSTEM.—Nematoda: *Filaria*, p. 305.

BLOOD.—Trematoda: *Schistosoma*, p. 239. Nematoda: *Filaria*, larvæ, p. 305.

MUSCLES.—Nematoda: *Trichinella*, p. 297.

SUBCUTANEOUS.—Nematoda: *Dracunculus*, p. 303; *Filaria*, p. 305; *Agamofilaria*, p. 314; *Rhabditis*, p. 303; *Gnathostoma*, p. 302. Insecta, p. 328.

ECTOPARASITES.—Acarina, p. 317. Insecta, p. 328.

NOMENCLATURE AND TERMINOLOGY

To the biologist, *nomenclature* deals with the *names* used to designate systematic units, such as families (*Taeniidae*), genera (*Taenia*), species (*Taenia saginata*), etc. As systematic zoölogists are obliged to use thousands upon thousands of such names, it is advisable that these should be removed, so far as possible, from the influence of individual or national tastes and prejudices; and, in order to make them international in character, Latin has been adopted as the basis for all *technical* names (as opposed to *vernacular* names). The acceptance or rejection of names and the method of writing them are governed by "codes of nomenclature." For the zoölogists, the International Congress has adopted an "International Code,"¹ prepared by a permanent international commission of eighteen members. This code is based primarily upon the rules proposed by Linnaeus, in 1751, modified to meet the advances in science. In order that no revolutionary principle may be suddenly introduced, the rules of the Congress provide that no proposition for changing the code can be adopted unless submitted to the Commission at least one year prior to the tri-annual meeting of the Congress. The chief points in the code are: (1) The "law of priority," which provides that the valid name for any genus or species is its oldest available name, *i. e.*, available under the code; thus, *Ascaris*, 1758, is an older name than *Fusaria*, 1800, for the eelworm. (2) The "rule of homonyms," which provides (*a*) that when two generically distinct animals have received the same generic name, this name is available only for the earlier genus

¹ See Stiles, 1905, pp. 1 to 50, the "International Code of Zoölogical Nomenclature as applied to Medicine." *Bulletin* 24, *Hygienic Laboratory*, U. S. Public Health and Marine Hospital Service, Washington. See also Proceedings of the Ninth International Zoölogical Congress of 1913.

(thus, when *Trichina* was proposed for a genus of worms by Owen in 1835, it was already in use for a genus of insects, 1832, hence the name cannot be adopted for the worm); and (b) that when two species in any given genus have received the same specific name, it is available only in its earlier use (thus, *Taenia murina*, 1845—*Hymenolepis nana*, 1852,—is antedated by *Taenia murina* Gmelin, 1790—*Cysticercus fasciolaris*—hence *murina*, 1845, is not available as a name for the dwarf tapeworm, and *nana*, 1852, its oldest synonym, becomes valid). (3) No name can be changed because of its inappropriateness or for any subjective reason, as *names are not definitions*, hence the introduction of *Amoeba dysenteriae* for *Amoeba coli* was not permissible under the code.

Physicians are urged to acquaint themselves with the rules, before they publish or change zoölogical names, as it is often difficult to understand whether or not a physician is using a new name in a zoölogical sense, and further, because names are too frequently proposed contrary to zoölogical customs.

Terminology, in distinction to nomenclature, deals with the technical *terms* of parts, organs, functions, conditions, etc. No recognized code of rules governs the names of the muscles of the body or the names of diseases. A man adopts a technical term because it has been taught to him, or he changes it, if a better name occurs to him, and, finally, men adopt the names best known to them. Thus, terminology is largely subjective, and such incongruities occur as using a term like "spotted fever" for two or three different diseases; while in the United States "typhus" refers to one disease, in Germany it is frequently used for another malady (typhoid).

For parasitic diseases we may distinguish three different kinds of terms in particular: (1) Latin terms based upon the zoölogical generic names (as *distomatosis*, *taeniasis*, *trichinosis*, *acariasis*, etc.); (2) vernacular terms based upon some symptom, geographical locality, etc. (itch, Egyptian hematuria); (3) vernacular terms based upon a vernacular name of the parasite (hookworm disease). For international use, Latin terms are by all means preferable, as they do not need to be translated, but for current use vernacular terms are often very convenient.

Bibliography.—In a short article of this kind it is impossible to give a full bibliography, for which the reader is referred to Huber's *Bibliographie der klinischen Helminthologie* (1895, 1898, 1899–1900), or Stiles and Hassall's Index Catalogue of Medical and Veterinary Zoölogy (*Bull.* 39, *U. S. Bureau of Animal Industry*), and Looss (1905).

For annual reviews of literature on parasites, see especially *Zoölogical Record* and *Archiv für Naturgeschichte*. For current literature, with original articles, reviews, and current bibliographies, see especially *Archives de Parasitologie*, *Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten*, *Zoölogischer Anzeiger*, and *Zoölogisches Centralblatt*. The current zoölogical references can be purchased in card form from the Concilium Bibliographicum, Zurich. The most extensive card catalogue on the subject is the combined index in the Zoölogical Divisions of the U. S. Public Health Service and the U. S. Bureau of Animal Industry.

Determination of Specimens.—Specimens of animal parasites of man are determined for physicians, free of charge, by the Division of Zoölogy, Hygienic Laboratory, U. S. Public Health Service, Washington, D. C. Such material should be forwarded in alcohol (about 50 to 70 per cent.).

Government Publications.—For U. S. Government publications on animal parasites, application should be made to the "Keeper of Public Documents, Washington, D. C.," or (either directly or through a Senator or Congressman) to the Chief of the Bureau by which the document was issued.

Laboratory Work in Colleges.—As many of the parasites of dogs, cats, rats, and swine are either specifically or generically identical with the parasites of man, fresh material for class work can be obtained from these animals. Fecal material, containing hookworm eggs, can frequently be obtained by writing to the U. S. Marine Hospital, Wilmington, North Carolina, or to the various Southern State Boards of Health.

DISTOMATOSIS-TREMATODE OR FLUKE INFECTIONS¹

Terminology.—The general term *distomatosis* or *distomiasis* is based upon *Distoma*, which has been used by many authors as the collective genus for the trematodes, more especially for the so-called digenetic forms. As a generic name for these parasites *Distoma* is not valid and the species which have been included in this genus are now distributed over a large number of well-defined genera. Upon the names of these more restricted genera, Latin terms have been based to designate infections with species of the respective genera (as *fascioliasis*, *clonorchiasis*, *opisthorchiasis*, *paragonimiasis*, *schistosomiasis*). The word "distomatosis" has been combined with the name of the organ affected (as pulmonary distomatosis); while for some of the diseases, there are well-known vernacular terms (liver-fluke disease, liver rot, etc.).

Trematode Diseases in Man.—There are four different clinical classes of trematode diseases which may be regarded as typical, in the sense that in these four instances the infection of man by certain trematodes is more or less normal in the life-cycle of the parasite under consideration. These are: (1) A pulmonary distomatosis, with cerebral or other infection as secondary; (2) an hepatic distomatosis, with splenic or intestinal infection as secondary; (3) an intestinal distomatosis; and (4) a venal distomatosis. In addition we find recorded rare instances of (5) an ophthalmic distomatosis, which may be an accidental secondary form of hepatic distomatosis.

All of the parasites in question, with the exception of the blood-flukes, are hermaphrodites, and possess an oral or an oral and a ventral sucker, a mouth, and two blind intestinal ceca. The life-cycle is quite complicated and may involve two or more generations which live outside of man. The parasites may require an intermediate host or in some cases direct infection may occur.

¹ For more detailed zoölogical descriptions, in English, of these parasites, see Stiles, 1904 i, pp. 1-66, Figs. 1-48; "Illustrated Key to the Trematode Parasites of Man." *Bulletin 17, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service*, Washington. For detailed index to subject, see *Bulletin 37, Hygienic Laboratory*, etc.

PULMONARY DISTOMATOSIS—LUNG-FLUKE DISEASE

Paragonimiasis or Parasitic Hemoptysis.¹—**Geographical Distribution.**—The Asiatic region, particularly Japan and China, appears to be the special home of this disease in man, although a generically related if not specifically identical infection occurs also as an endemic disease in hogs in the United States. It is reported also for the Philippines, Formosa, and Korea, and occasionally imported cases are found in other places.

Zoölogical Distribution.—It is difficult to determine the original host of this disease but it is known to occur more or less frequently in man, cats, tigers, dogs, swine; and Looss (1905) says it occurs in cattle. Pulmonary distomatosis is occasionally found in cattle as an accidental manifestation of fascioliasis, and lung infection with other genera of flukes is exceedingly common in snakes, toads, and frogs.

The Parasite.—*Paragonimus westermanii*² (Kerbert, 1878) is a plump, depressed, oval, or pyriform, pinkish to reddish-brown (live specimens), spinose fluke, 7.5 to 16 mm. long by 4 to 8 mm. broad by 2 to 5 mm. thick; with branched testicles and ovary but unbranched intestinal ceca; eggs yellow, 77 to 102.5 by 40 to 75 μ with distinct operculum but containing no miracidium when discharged. The adult parasites are found in cysts, one to three together, in the lungs, especially in upper lobes, occasionally in the pleura, liver, abdominal cavity, brain, orbit, lower eyelid, cervical glands, scrotum, and other parts of the body.

Source of Infection.—Unknown. The eggs develop a ciliated miracidium (embryo) in water in four to eight weeks; this probably enters some snail. The infecting stage probably enters man with contaminated food or water; Katsurada thinks it may pass directly from the mouth to the bronchi, or if swallowed, from the stomach up the œsophagus and down into the lungs, or perhaps from the stomach through the stomach wall to the mesenterium and from there by the lymphatics to the final point of rest.

Frequency.—More frequent in mountainous localities (Katsurada); chiefly in peasants, more common in males than in females (88.57 per cent. to 11.43 per cent. in 481 collated cases) and between the ages of sixteen and thirty years; in some localities 20 to 73 per cent. of the lung-fluke patients give a history of other cases in the same family (Katsurada), while in other places the family history is reported as negative. It is stated that in certain parts of Formosa, 15 per cent. of the inhabitants are affected; in one Japanese village nearly all the inhabitants harbor the parasite (Baelz). In a hospital in Okayama, 0.4 per cent. of the 20,793 patients from 1891 to 1897 showed infection (Inouye). Various Japanese physicians report that from 2 to 14 per cent. of their patients

¹ For a more detailed discussion in English, with bibliography, see Stiles and Hassall, 1900, pp. 560 to 611.

² SYNONYMS.—*Distoma westermanii* Kerbert, 1878; *D. ringeri* Cobbold, 1880; *D. pulmonis* Kiyoma, Suga, and Yamagata, 1881; *D. pulmonale* Baelz, 1883; *D. pulmonum* (Baelz) Tomono Hidekata, 1883; *D. cerebrale* Yamagiwa, 1890. In the lists of synonyms given in this paper, only the more common or the newer names are mentioned; for full lists of synonyms the reader is referred to the special literature on the various species.

suffering from respiratory troubles harbor this fluke. Inouye (1903) has collected 19 cases of brain infection. From 2 to 28, perhaps more, parasites occur in each patient.

Duration.—The longevity of the individual parasite is not established but cases are reported with histories extending over ten, twenty, and even thirty years; these are probably due to repeated infections.

Pathology.—(a) *Lung Infection.*—Occasionally deep, more commonly superficially in the lung, or directly under the pleura, are found roundish or flat cysts about as large as the end of the little finger, and containing from one to three parasites or in some cases only caseous contents. Katsurada (1900) is of the opinion that these cysts represent dilated bronchi, although he does not deny that cavities in the lung tissue may form independently of the bronchi; the lumen communicates with the neighboring bronchi by one large or numerous small openings and the different cysts may communicate with each other by means of direct or long irregular tubes; the septa between the tunnels may break down and a considerable cavity be thus formed (Manson); the wall of the cyst is rather stout, grayish white, about 1 mm. thick; the inner surface is usually smooth, and the lumen may contain a reddish or brownish-green, slimy fluid. When the worms settle in the bronchi, the walls undergo an inflammatory infiltration, a richly vascularized granulation with connective-tissue forms, and the original structure of the bronchi becomes lost. The bronchitis is caused not only by the worms but also by their eggs. An adhesive pleuritis may develop.

(b) *Brain Infection.*—Yamagiwa reports disseminated circumscribed foci of trematode eggs, usually also with giant cells, in the cortical substance of the occipital, parietal and central lobes of the brain; surrounded by connective tissue and round-cell infiltration; thickening of the wall of the bloodvessels, especially of the adventitia, and obliteration of some of the branches.

Symptoms.—These vary with the location and number of the parasites.

(a) *Lung Infection, Parasitic Hemoptysis.*—This is the usual and uncomplicated (primary) form and represents the typical paragonimiasis or pulmonary distomatosis as found in man. The onset may be so gradual that the beginning cannot be recognized with certainty. The only constant and specific characteristic is the presence of the eggs in the sputum; it is estimated that as many as 12,000 ova may be expectorated daily. The *sputum* is yellow to red or rusty brown, due to the presence of the microscopic eggs, and has a peculiar odor, partially due to blood; poor in water and rich in mucus, it varies from a small amount to 100 cc. daily; blood is common but not constant, being present in points, strings, or larger amounts; while severe hemorrhages are not common, Baelz reports a case with a loss of a pound of blood within a few hours; intense anemia may result; the sputum is often discharged in spirals, resembling Curschmann's spirals, and contains eggs, blood, pus, mucus threads, alveolar and bronchial cells, numerous Charcot's crystals; Taylor and Mimachi have each observed an expelled worm. There may be hoarseness or a chronic cough, usually light, rarely so severe as to disturb sleep and most urgent in the morning upon rising.

As the disease progresses the periods of cough and hemoptysis become more frequent and prolonged, tending more or less toward permanency and the amount of expectoration increases from a slight quantity at the onset to a much greater quantity later—as much as 10 to 12 ounces in a few hours. All symptoms increase after physical exertion. Physical examination does not usually reveal anything abnormal except in severe cases; as the patient fails, auscultation shows diminished respiratory murmur, the breath-sounds being vesicular but rarely weak, occasionally bronchial in character with dry or moist rales. Inouye reports unilateral or bilateral signs appreciable on percussion in 86 per cent. of 92 patients examined; only 1 of these had tuberculosis. The temperature is normal or but slightly elevated, even in severe cases. The patient may become exhausted by cough and hemorrhage; he also becomes deeply anemic, and suffers from dyspnoea on slight exertion. Slight œdema often occurs. After rest in bed all symptoms may abate except the cough and expectoration, and months may pass before a relapse occurs. Gradually the constitution becomes undermined, convalescence becomes less complete, periods of rest become shorter, those of prostration longer and more severe, œdema and anemia increase, and at last the exhausted patient dies.

FIG. 9



Egg of lung-fluke showing ovicell, yolk cells, and operculum. $\times 100$. (Katsurada.)

The *lethality* of the uncomplicated form does not seem to be established, but it doubtless varies with the intensity of the infection.

(b) *Brain Infection*.—If the worms or their eggs gain access to the brain, a *cerebral distomatosis* develops, resulting in epileptiform attacks (Jacksonian or cortical epilepsy). It does not appear to be established in what percentage of cases this occurs, but it is an extremely serious and fatal form. The epileptic attacks may at first be a month or so apart, but they gradually increase in frequency and severity until death.

(c) *Infection in Eyelid*.—Several cases have been reported in which the parasite lodged in the eyelid, forming a tumor which resulted in obstruction to the sight and to movement of the eye.

(d) *Liver Infection*.—A purely accidental hepatic distomatosis may occur in connection with pulmonary distomatosis, in that eggs of the lung-fluke may be found in the liver. Such occurrence, however, can hardly result in a typical hepatic distomatosis and it is possibly an open question whether some of these cases were not due to the newly recognized Japanese blood-fluke (see p. 239).

(e) *Infection of Other Organs*.—Cysts of lung-fluke eggs may also occur in the mesentery, omentum, etc., but thus far such lesions do not appear to have produced any serious symptoms.

Clinical Diagnosis.—The disease was long confused with tuberculosis, from which it may be readily distinguished by microscopic examination of the unstained sputum to find the characteristic egg.

Treatment.—No specific treatment is known. Inhalations have proved unsatisfactory. By sending the patient to an uninfected locality further infection is avoided, and with the lapse of time (the length of which is not known) the parasites may finally die and become disintegrated or may be coughed up. Surgical interference has been suggested for cases in which the parasite can be definitely located.

Prevention.—(1) Destruction of infected sputum; destruction of cats and dogs showing the same disease; destruction of the lungs of swine showing the same infection. (2) Use of filtered or boiled drinking-water; thorough washing of vegetables; thorough cooking of snails when these are used for food. These latter precautions are based upon analogy, as nothing positive can be stated in this line until the life-history of the parasite is known.

Pulmonary Distomatosis Due to *Fasciola Gigantica*.—One case of pulmonary distomatosis in man has been reported as due to *Fasciola gigantica*. This was doubtless a case of chance parasitism, as man is not known to be a normal host for *Fasciola*, and as the liver, not the lungs, is the normal organ in which *Fasciola* occurs. The parasite in question is common in Africa in the liver of buffalo, cattle, sheep, and goats; it was originally described for the giraffe; it is similar to *F. hepatica* in structure, but much narrower, measuring 25 to 75 mm. long by 3 to 12 mm. broad; eggs 145 to 190 by 75 to 90 μ .

HEPATIC DISTOMATOSIS—LIVER-FLUKE DISEASE

At least six different species of liver-flukes, representing three different genera (*Clonorchis*, *Opisthorchis*, *Dicrocoelium*, and *Fasciola*), have been found in connection with hepatic distomatosis. Infections with *Clonorchis* are common to man, dogs, and cats, and are much more frequent in man than are infections with *Dicrocoelium* and *Fasciola*, which man has in common with certain food animals, particularly cattle and sheep. Of the six specific infections in question, one (an Asiatic disease) is much more important than all the rest combined.

Source of Infection.—For only three of these infections—namely, for the fascioliasis, due to *Fasciola hepatica*; clonorchiasis, due to *Clonorchis endemicus*, and opisthorchiasis, due to *Opisthorchis felineus*—is the source of infection known (see pp. 230, 233), for all of the others this is a matter of speculation, based upon analogy and circumstantial evidence.

Clinical Diagnosis.—This is identical for all six infections. Make a microscopic examination of the unstained feces for eggs; also of the sputum and urine, as the ova in pulmonary and venal distomatosis may be discharged per anum; hence, finding eggs in the feces, without excluding pulmonary and venal distomatosis, may lead to error.

Treatment.—There is no specific treatment for any form of hepatic distomatosis; remove the patient to a non-infected area, or, if he be kept at home, avoid further infection and give good, nourishing food.

Prevention.—The same general principles apply to all six infections.

CLONORCHIASIS

Asiatic Clonorchiasis or Japanese Liver-fluke Disease.—**Geographical Distribution.**—This infection is endemic in Asia, more especially in Japan and China, but it is also found in the Philippines, India, Formosa, Mauritius, Annam, Tonkin and Korea. About twenty imported cases have been recorded in the United States.

Zoölogical Distribution.—So far as can be judged at present, man must be considered one of the normal hosts, but cats and dogs also appear to be normal hosts, and the infection occurs in swine.

The Parasite. Asiatic liver-fluke disease is caused by elongate, lanceolate, non-spinose trematodes,* belonging to the genus *Clonorchis*, characterized by the branched condition of the caudally located testes; the eggs are dark brown, with sharply defined operculum, occasionally with small knob at posterior end, and contain a ciliated miracidium at oviposition. There is a slight difference of opinion at present whether all of these worms belong to a single species (*C. sinensis*) or to two distinct species (*C. sinensis* and *C. endemicus*).

C. sinensis, sensu str.,¹ is said to be found only in man; endemic in China and Japan, usually present in small numbers comparatively harmless, and measures 13 to 19 by 3 to 4 mm.; its eggs measure 26 to 30 μ by 15 to 17 μ .

*C. endemicus*² is reported for man, dogs, cats, and swine, from Japan, Tonkin, and Annam, is said to be present in larger numbers, and to be more harmful; it measures 6 to 13 by 1.8 to 2.6 mm., and its eggs are 26 by 13 to 16 μ . The adult worms inhabit particularly the gall-ducts, but may be found in the gall-bladder and in the pancreatic duct and (probably in the act of wandering), also in the duodenum and stomach. Katsurada (1900) found them in the pancreas in 9 out of 67 infections.

Source of Infection.—*C. endemicus* is contracted from eating raw fish, especially *Pseudorasbora parva* and *Leucogobia güntneri*.

Frequency. According to Taylor, some native practitioners in the infected villages estimate that 1 in 7 or 1 in 5 of the entire local population is infected, and where one member of a family is infected several members are likely to harbor the worm. Katsurada (1900) recognized 654 cases of infection in 1075 persons examined (60.8 per cent.) in three villages engaged chiefly in rice culture and in a region abounding in canals with dirty water. It is said that in Japan, in certain regions where the water is poor, 20 per cent. of the inhabitants are infected, while in localities a few miles distant and with better water the parasite is comparatively rare. In some patients only a few parasites are present, while

¹ **SYNONYMS.**—*Distoma sinense* Cobbold, 1875; *Distomum spatulatum* Leuckart, 1876 (not Creplin, 1849, for *D. spatulatum* Rudolphi, 1819); *D. spatulatum* Cobbold, 1879 (not Rudolphi, 1819); *D. hepatis inoocum* Baelz, 1883; *Opisthorchis sinensis* pars of authors; *Dicrocoelium sinense* (Cobbold) Moniez, 1896; *C. sinensis major* Verdun and Bruyant, 1908.

² **SYNONYMS.**—*Distomum hepatis endemicum* s. *perniciosum* Baelz, 1883; *D. japonicum* R. Blanchard, 1886; *C. sinensis minor* Verdun and Bruyant, 1908; *C. sinensis* pars of authors.

in others large numbers are found. Thus, Katsurada (1900) reports that of 72 cadavers examined, 4 contained from 2216 to 4361 worms each, and Blanchard (1901) reports 1 infection with over 10,000 parasites.

Duration.—Cases of infection of two to five years' standing seem to be common, but the longevity of the individual parasites does not seem to be determined.

Pathology.—As the parasites are situated chiefly in the liver, we naturally expect this to be the chief seat of the lesions; in fresh cases it is enlarged, sometimes hyperemic, in prolonged cases normal or decreased in size and more or less cirrhotic. The superficial gall ducts are prominent, white, opaque, and irregularly thickened; worms may be pressed out singly or in bunches in the thick, slimy, yellow to dark brown bile. The lesions are particularly of two kinds, involving the biliary canals and the hepatic parenchyma. When the worms enter the bile canals they obstruct the lumen more or less completely; the first result is a bile stasis with resulting dilatation of the canals; the latter acquire considerable dimensions, while both epithelial and subepithelial layers undergo profound modifications. Opinion has been expressed that these changes are due to mechanical causes; without doubt these are important, but the parasites seem to do other damage than acting simply as foreign bodies, for in case of infection with *Fasciola hepatica*, Railliet has shown that the parasites suck blood from the capillaries in the walls of the canals. The lining of the ducts shows catarrhal irritation; the discharged mucus contributes to the occlusion of the canals; the glands undergo considerable hypertrophy which increases progressively and develops an extended adenoma; the newly formed bile canaliculi are numerous at the side of the chief canal with which they communicate; in sections nodules of several millimeters in thickness may be found which contain sections of a number of canals. The connective-tissue layer of the canals undergoes very active proliferation and may attain an enormous thickness, its outer layer showing more or less small-cell infiltration; it pushes before it the epithelium and thus contributes to the obliteration of the canal; it also compresses the hepatic tissue, at the expense of which it lodges and which then undergoes secondary lesions. A cirrhosis develops which, with time, acquires considerable proportions. The hepatic tissue undergoes granular and fatty degenerations and, little by little, atrophies. The lesions have a marked influence on the general nutrition; the arrest of bile causes digestive trouble; compression of the branches of the portal vein causes stasis toward its origin from which ascites results (Blanchard, 1901 c). The gall-bladder may be greatly enlarged. The spleen was enlarged in 6 of the 15 cases in which ascites was present, but in 1 case this organ was considerably reduced in size. Of 76 cases, 9 (11.8 per cent.) either showed or gave a history of icterus; of the 15 cases with ascites, icterus was present in 7 (46.6 per cent.).

Symptoms.—To a certain extent these depend upon the number of parasites present, so that light infections may escape attention unless a microscopic examination is made. Usually there is at first increased, exceptionally decreased, appetite. In heavy infections, one of the first

and most pronounced symptoms is the enlargement and tenderness of the liver, preceded, attended, or followed by diarrhœa; the stools become irregular; the diarrhœa is at first irregular and intermittent, the attacks becoming more and more frequent and prolonged, until after two to five years there may be hardly any interval between them; the stools may be light, or dark and bloody, and may reach twelve per day; in some cases blood is present only at irregular intervals, in others the bloody diarrhœa becomes almost constant. The liver continues to increase in size, in some cases reaching the navel, though at times it apparently diminishes temporarily; there may be tenderness over the hepatic region or more or less dull pain and pressure may result in excruciating agony; jaundice, sometimes intermittent, is a frequent symptom; there is

FIG 10



Egg of Asiatic liver-fluke greatly enlarged
(Katsurada)

generally a dark, ashen discoloration of the skin. The temperature may be normal or may increase to 100° F. After a time anasarca, likewise intermittent, appears and affects the legs especially. Night blindness is likely to occur. Epistaxis is rather common. Ascites often occurs, may increase for a time, then gradually diminish, to appear again and again. The patient is reduced by diarrhœa, becomes emaciated and grows anemic and weak, but the appetite is usually preserved. It frequently happens that the patient is reduced so low that life is despaired of, yet he may gradually rally and apparently become almost well (Taylor, 1884). Later, however, relapse occurs, and

the same process is repeated again and again, ground being lost each time, until at length, worn out and exhausted, the patient dies after many years of illness.

Lethality.—Of 1495 cases, compiled for the province of Okayama, Katsurada (1900) reports 238 as fatal (16 per cent.).

Clinical Diagnosis.—Microscopic examination of unstained feces to find the egg of the parasite is necessary. When in an infected locality a case of enlargement of the liver and bloody diarrhœa is seen, careful examination of the feces usually shows the eggs.

Treatment.—No specific treatment is known. Whether any severe cases ever fully recover is not stated, but it seems, *a priori*, that a change of locality to uninfected districts, thus preventing further infection, should be attended by at least a prolongation of life. Katsurada (1900) suggests the advisability of laparotomy in some cases, in order to press the parasites out of the gall-ducts into the intestines.

Prevention.—(1) Destruction of all cats and dogs affected with the parasites, and disinfection, by heat or by drying, of all feces from infected persons. (2) Avoid eating raw or undercooked fish.

OPISTHORCHIASIS

The term opisthorchiasis was introduced by Looss (1905) to designate infection with flukes belonging to the genus *Opisthorchis*, a group

characterized chiefly by the position of the unbranched testes near the posterior extremity of the body. In man we may distinguish at present two distinct infections by species of this genus; in order of importance these are the European and the Indian species.

Siberian Opisthorchiasis or Siberian Liver-fluke Disease.—**Geographical Distribution.**—The parasite is reported for France, Germany, Holland, Italy and Russia, but cases in man are known only for Prussia (Germany) and Siberia. The report of this parasite in the United States is based upon a misdetermination (*Opisthorchis pseudofelineus*).

Zoölogical Distribution.—The cat, and possibly the dog, the fox (*Vulpes vulpes*), and the glutton (*Gulo borealis*) form the natural hosts for this infection; it is not yet thoroughly established whether man is a natural or a chance host, though indications point to the latter.

The Parasite.—This particular infection is caused by the European cat-fluke (*Opisthorchis felineus*), a lanceolate, non-spinose worm, measuring from 8 to 15, rarely to 18 mm. long by 1.25 to 2.5 mm. broad; the testes are lobate, but not branched; eggs oval, yellow brown, 26 to 30 by 11 to 15 μ , one side slightly flatter than the other; with sharply defined operculum on the more acute pole and containing a ciliated miracidium at oviposition. The adult parasites inhabit the gall-ducts, but are occasionally found in the pancreas and duodenum.

Source of Infection.—The embryo does not hatch in water, but it hatches in snails belonging to the genus *Limnaea*, although it does not develop further in this host. Suspicion has fallen upon raw fish as a source of infection, and Askanazy (1906) has traced the infection to the dace (*Leuciscus rutilus*) and the ide or orf (*Idus idus*).

Frequency.—This is an exceedingly common parasite of cats in some parts of Europe. Winogradoff (1892) reports 8 cases of infection (6.45 per cent.) in man in 124 autopsies as Tomsk, Siberia; Rindfleisch (1910) reports in all 40 cases, during nine years, in the Königsberg clinic; and Kurimoto (1900) and Kholodovsky are authority for 1 case in St. Petersburg, Russia, in a patient who had been in Siberia; infection in man is recorded for Tonkin, also. In the cases reported for man, there were several to a thousand (Askanazy, 1901) parasites present.

Winogradoff has reported an additional case of infection with a small spinose fluke which he supposed was a young *O. felineus*. Braun has pointed out that this might perhaps be a *Pseudamphistomum truncatum*, a small spinose fluke which occurs in the dog, cat, fox, glutton, and seal.

Pathology.—In general this is similar to that of Asiatic clonorchiasis, except that no such severe infections have been studied. Askanazy (1900*b*) summarizes the pathology as cholangitis catarrhalis and pericholangitis fibrosa or as Virchow described it in fascioliasis, as a chronic choleporitis and fibrous periportitis. Bossuat (1902) summarizes the condition as an irritation of the walls of the biliary canals, a thickening with pisiform dilatations, followed by a veritable cirrhosis.

Duration.—Unknown. In one case probably nearly three years.

Symptoms.—The cases that have been found have not all been carefully studied clinically. In general, approximately the same clinical picture

may be expected which is found in corresponding infections with the Asiatic fluke, for the worms are very closely related and the lesions more or less identical. According to Askanazy (1900 b), Winogradoff reported icterus in 5 of his cases, decreased liver in 5 cases, enlarged liver in 2 cases, ascites in 3 cases.

Lethality.—In none of the cases reported is the parasite given as the direct cause of death.

Clinical Diagnosis and Treatment.—See p. 232.

Prevention.—See p. 232. In view of the fact that fishes form the intermediate host, it will be well to avoid eating raw fish.

Indian Opisthorchiasis or Indian Liver-fluke Disease.—**Geographical Distribution.**—Thus far reported only for Calcutta, India, unless Winogradoff's ninth case (which Braun thinks may perhaps have been due to *Pseudamphistomum truncatum*) belongs here (?).

Zoölogical Distribution.—Man and dogs. It is not yet known whether these are normal or merely chance hosts. The view that this parasite occurs in the North American red fox (*Canis fulvus*) is based upon an error of identification.

The Parasite.—The Indian liver-fluke, *Opisthorchis noveca* Braun, 1903, is a lanceolate, spinose fluke, 9 to 12.5 mm. long by 2.5 mm. broad, which lives in the gall ducts. Eggs oval, 34 by 19 to 21 μ .

Symptoms.—In general, these are probably the same as for other species of this genus, see p. 231.

Source of Infection, Duration, Lethality, and Prevention.—Unknown.

Frequency.—Only two cases (McConnell, 1876 and 1878) known.

LANCET FLUKE INFECTION

Geographical Distribution.—This infection seems to be primarily one of Continental Europe. Its exact distribution cannot be stated, as there has been considerable confusion in the determinations of infections with this and other lanceolate parasites. Aside from Europe, it is reported for Northern Africa, Siberia, Turkestan, and North and South America. American specimens have not been seen by the writer.

Zoölogical Distribution.—The same confusion also exists in reference to the hosts. Apparently cattle and sheep are the normal hosts for this worm, which is also reported for the goat, deer (Hirsch), horse, ass, hog, hare, rabbit, and man. Certainly many and possibly all of the reported occurrences of this infection in carnivorous animals (dogs and cats) are based upon errors of identification.

The Parasite.—The lancet fluke (*Dicrocoelium lanceatum* Stiles and Hassall, 1896) is a non-spinose, lanceolate trematode, 4 to 9 mm. long by 2 to 2.4 mm. broad, characterized by the anterior position of the testes, which are between the acetabulum and the ovary, and by the posterior position of the uterus. Eggs, dark brown, thick-shelled, 38 to 45 by 20 to 30 μ , with a distinct operculum and containing a ciliated miracidium when oviposited; the embryo is provided with two dark spots in the posterior portion.

Source of Infection.—Unknown. Embryos hatch in the intestine of slugs (Arionidæ) but not in water; they do not, however, develop further in these mollusks.

Frequency.—While the parasite is quite common in cattle and sheep, only 7 cases of its occurrence in man have been reported. It is doubtless purely an accidental parasite for man.

Duration.—Unknown.

Symptoms, Lethality, and Pathology.—Probably not serious, as only light infections are likely to occur in man. Kirchner reports 1 case with gall-stones. It seems not impossible that Mehlis' case, in which a woman vomited 50 specimens of this parasite and 9 of *Fasciola hepatica*, resulted from eating infected liver which was not thoroughly cooked.

Clinical Diagnosis, Treatment, and Prevention.—(See p. 229.)

FASCIOLIASIS—INFECTION WITH FASCIOLA

Fascioliasis is, properly speaking, distomatosis caused by species of the genus *Fasciola*. While the liver is the normal habitat for these worms, it occasionally happens that fascioles infest other parts of the body. In man fascioliasis is probably always due either (1) to a purely chance infection by the larvæ which then develop in the liver, or, in rare cases, some other part of the body, as the lungs (p. 229), the eye (p. 245), or the veins (*Hexathyridium venarum*), etc.; or (2) to accidental infection with the adult worm, due, as Khouri (1904) has recently shown, to eating raw liver containing these parasites.

Geographical Distribution.—The common liver-fluke is reported with a very wide distribution, but as the parasites on different continents are studied more carefully it is found that the infections alleged to be due to this species are specifically distinct, although generically identical. On account of these changes in ideas regarding classification this entire subject must be restudied. Europe is to be considered the type locality of *Fasciola hepatica*, and the same parasite seems to occur in North America and Australia. It is reported also for Asia, Africa, and South America.

Zoölogical Distribution.—This infection is reported from more animals than are probably actually infected with it but its normal hosts seem to be cattle, goats, and sheep; it is also reported for many other animals.

The Parasite.—*Fasciola hepatica*¹ Linnaeus, 1758, is a flat, leaf-like, spinose worm measuring 18 to 30 mm. (reported to 51 mm.) long by 13 mm. broad; the intestine, testes, ovary, and vitellogene glands are profusely branched. Eggs, yellow-brown, oval, 130 to 145 by 70 to 90 μ , with distinct operculum, not containing embryo when oviposited.

Source of Infection.—Snails of the genus *Limnaea* (*L. truncatula*, *L. oahuensis*, *L. rubella*) form the intermediate host, and infection takes place normally by swallowing the cercaria which encyst on plants in marshes.

¹ SYNONYMS.—*Distoma hepaticum* (Linnaeus) Abildgaard; *Fasciola humana* Gmelin, 1790; *Hexathyridium venarum* Treutler, 1793.

Frequency.—While this infection is rather common in cattle and sheep, especially those pasturing in marshy districts, it seems to be purely accidental in man. Not every case reported as *Fasciola hepatica* is to be accepted as such. One source of error is to mistake single segments of tapeworms for liver-flukes; the writer has seen several cases in which this had been done. Blanchard has carefully collated the authentic cases reported for man and Moniez has added several to Blanchard's list. One recent case for Porto Rico is known to the writer; but while the parasite is a *Fasciola*, it seems to represent a new species. Cases have been reported for the blood and in subcutaneous tumors.

Attention may be directed to the fact that the eating of raw liver infected with *F. hepatica* may be a much more serious matter than has heretofore been supposed and may cause in man a condition which, in certain localities at least, is apparently more common than is the presence of the common liver-fluke in the human liver.

Halzoun.—According to Khouri (1904) there exists in northern Liban, Syria, a disease known as "halzoun," which he attributes to *Fasciola hepatica* contracted through eating raw goat-liver infested with the parasite. His experiments upon rabbits, as well as clinical observations, indicate that the parasites attach themselves to the pharyngeal mucosa where they gorge themselves with blood after the manner of leeches; Khouri thinks that the parasites may secrete a substance which acts as a vasodilator. After gorging themselves with blood the flukes loosen their hold, reach the stomach, and are expelled with the vomit. There are two sets of symptoms; namely, congestive (a more or less intense œdematous congestion of the buccopharyngeal mucosa, of the larynx, nasal fossæ, tonsils, Eustachian tube, ear, conjunctivæ, and lips) and mechanical (dyspnoea, dysphagia, aphonia) resulting from the first phenomena.

Symptoms.—After eating the infected raw liver, the patient experiences an itching sensation deep in his throat; soon he feels more or less malaise; the itching increases, extending to the ears and becoming painful; a buzzing in the ears follows and a sensation of auricular tension exasperates the patient. Two or three hours after onset the itching lessens; deglutition and dysphagia become painful; dysphonia develops and may extend to complete aphonia. The most alarming symptom is the dyspnoea, varying to orthopnoea in severe cases or asphyxia in fatal cases. The aspect is typical; the face is congested, the lips thick, cyanotic, and livid; an abundant saliva flows; the eyes are highly congested and there may be lachrymation; the conjunctivæ are injected and œdematous; photophobia and exophthalmia are common; the sight remains normal. In severe cases the neck is swollen and œdematous; palpation shows a variable submaxillary and cervical adenopathy and a diffuse puffiness; the œdema invades the cervical cellular tissue, in serious cases extending to the clavicle. Examination of the throat shows congestion and a more or less intense œdema of the pharyngeal mucosa of the palate and especially of the uvula and tonsils; the latter

¹ Arabian word for spiral or snail.

are considerably enlarged and, in severe cases, may meet in the median line, leading to asphyxia. Laryngoscopic examination shows an unusually narrowed superior larynx, of red-violet color, the vocal cords are slightly œdematous, but the opening of the glottis is not seriously restricted. There is rather an intense reddening of the external auditory canal and especially of the tympanum.

The temperature usually remains normal but the pulse increases with the dyspnœa. Examination of the lungs and urine is negative.

Besides the common form, described in the foregoing, one may distinguish light, grave, and fatal cases. In the light cases, dysphonia and distinct dyspnœa are not observed; the duration is short, varying from a few hours to two or three days. In the grave form the symptoms reach their maximum; the incubation is only five to twenty-five minutes; after ten to eighteen hours, the pharyngolaryngeal symptoms are intense; if the symptoms do not ameliorate by the end of thirty-six hours, to continue for four or five days in benign form, death is inevitable; usually this attack lasts five to eight days.

Complications.—As complications may be found: abscess, especially in the external auditory canal and in the mastoid region, suppurative otitis media, followed by perforation of the tympanum, and peripheral facial paralysis which disappears after eight or ten days.

Duration.—Attacks vary in length from a few hours to ten days. Most patients recover, death being exceptional.

Diagnosis.—As a rule this is not difficult but some cases may be confused temporarily with diphtheria, œdema of the glottis, cardiac or pulmonary dyspnœa, and acute iodism.

Treatment.—Vomiting dislodges and expels the parasite, and should be encouraged; it is more effective if the stomach is well filled.

Prevention.—Avoid eating raw liver.

INTESTINAL DISTOMATOSIS

The entire subject of intestinal distomatosis in man needs a careful restudy. Undoubtedly the infections are much more common than is ordinarily assumed, but we cannot as yet say for which infections man forms a normal and for which an accidental host.

Geographical Distribution.—So far as the writer has records, intestinal distomatosis in man is reported only of Asiatic and African origin.

Zoölogical Distribution.—Similar infections, some of them generically, and a few of them specifically, identical with those found in man, are exceedingly common in other animals.

The Parasites.—Intestinal distomatosis in man may be caused by the following flukes:

Fasciolopsis Buskii (Lankester, 1857). This is the largest and perhaps the most important of the intestinal flukes of man; thus far cases are known only of Asiatic origin (India, Assam, Siam, China, Straits Settlements, Sumatra), but Moore and Terril (1905) have reported one imported case in the United States, and Nicoll (1910) reports a case for

Natal. It measures 27 to 37 mm. (or even 75 mm., after Bask) long by 5.5 to 12 or 14 mm. broad, and 1.5 to 2 mm. thick. While not unlike the common liver-fluke (*Fasciola hepatica*) in superficial appearance, it can be easily distinguished from that form by its very large acetabulum and by its simple intestine. The eggs measure 120 to 130 by 77 to 80 μ with very delicate operculum. The life-history and source of infection are unknown. Infection with this parasite is reported as accompanied by indigestion, nausea, headache, and severe diarrhœa with bloody stools. The worms are said to be expelled by thymol or calomel.

Fasciolopsis Rathouisi (Poirier, 1887).—This trematode has been reported three times in the Asiatic region; in one case it does not seem to have been definitely established whether the worm was in the intestine or in the liver; the patient is said to have had "severe body pains." The parasite measures 25 mm. long by 16 mm. broad; eggs ovoid, 150 by 80 μ . The life-history and source of infection are unknown.

The systematic value of other species (*F. fülleborni*, *F. goddardi*, Kwan's fluke) of this genus may be considered as *sub judice* pending the publication of further studies now reported as in progress.

Echinostoma (Fascioletta) ilocanum (Garrison).—This parasite has been found 5 times in examination of 5000 persons in the Philippines; all the infected individuals came from Luzon; the medical significance of the worm is *sub judice*. The worm measures 4 to 6 mm. long by 0.75 to 1.37 mm. broad; eggs 88.8 to 114.7 μ long by 53.5 to 81.9 μ broad, miracidium not developed at time of oviposition. *Echinostoma* sp. is reported by Leiper (1911) in man in the Malay States.

Heterophyes heterophyes (Siebold, 1852).—This is a minute trematode, 1 to 1.7 mm. long by 0.3 to 0.7 mm. broad, found in the middle third of the small intestine of man, dogs, and cats in Egypt and reported once for Japan. Its chief anatomical characteristic is the presence of a sucker-like disk surrounding the genital pore; the acetabulum is much larger than the oral sucker. The eggs are light brown, thick-shelled, oval, 20 to 30 by 15 to 17 μ , with distinct operculum, and containing ciliated miracidium when oviposited. The life-cycle and source of infection are unknown. It seems to be entirely harmless in man (Looss).

Gastrodiscus hominis (Lewis and McConnell, 1876).—This fluke, originally described as *Amphistoma hominis*, occurs in the cecum and colon of man in India and has also been reported for East Indian immigrants in British Guiana. Braum is of the opinion that it is undoubtedly only a chance parasite in man and that its normal host is some Indian mammal. Indications are, however, not lacking that it is a more common parasite in man than has been supposed. Not less than four cases are now on record. The worm measures 5 to 8 mm. long by 3 to 4 mm. broad and when fresh is of a reddish color; the body is divided into an anterior, rather slender, conical portion and a posterior flattened, ventrally concave disk with small ventral acetabulum at the posterior end. The eggs measure 150 by 72 μ and possess an operculum at the narrower end; the miracidium is not formed before oviposition. The life-history and source of infection are not known.

Watsonius watsoni (Conyngham, 1904) Stiles and Goldberger, 1905.—This is an 8 to 10 mm. long amphistome reported once from the small intestine of a negro boy from Adamawa, German West Africa.

VENAL DISTOMATOSIS—BILHARZIOSIS¹—BLOOD-FLUKE INFECTION

Geographical Distribution.—Africa, Asia, Panama, Cuba, and Porto Rico; probably more generally as a tropical and subtropical disease. Occasional cases, chiefly imported, are recorded for the temperate climates; several cases have been recognized in the United States.

Zoölogical Distribution.—The Asiatic blood-fluke is reported for cats, dogs, horses, and cattle, as well as man. An infection occurs in the sooty monkey, which may perhaps be identical with the African blood-fluke. Generically identical but specifically distinct infections occur in horses, cattle, and sheep.

The Parasites.—Bilharziosis in man may be due to either of two (or three ?) distinct species of trematodes, the African blood-fluke and the Asiatic blood-fluke.

The African blood-fluke, *Schistosoma haematobium*² (Bilharz, 1852), so far as records are published, is the more common of the two; it occurs chiefly in Africa and adjacent islands but extends to Persia, Arabia, India, Panama, Cuba, and Porto Rico, and is occasionally found elsewhere. The male is 4 to 15 mm. long by 1 mm. broad; the sides are curved ventrally to form the gynecophoric canal; the worm is armed with numerous spinose warts. The female is filiform, 15 to 20 mm. long and lives in the gynecophoric canal of the male. The eggs are oval, 135 to 160 μ long by 55 to 66 μ broad, and are provided with a terminal,³ or lateral, subterminal spine, but not with an operculum.

The Asiatic blood-fluke, *Schistosoma japonicum*⁴ (Katsurada, 1904) has only recently been discovered (Japan, China, the Philippines and South Africa) and its frequency and distribution are not yet established, but it is known to be rather common in some localities. The male measures 7 to 12 mm. long by 0.53 mm. to 0.8 mm. broad; it is not armed with spinose warts; gynecophoric canal present. The female measures 8 to 12 mm. long. The eggs 60 to 90 by 30 to 50 μ , and are not provided with the terminal or subterminal spine nor with an operculum; near one pole, however, they show a small knob.

¹ SYNONYMS.—Egyptian hematuria; endemic hematuria; bilharzian hematuria; bilharzia disease. See especially Looss, 1905, Manson, 1903, and Milton, 1902.

² SYNONYMS.—*Distomum haematobium* Bilharz, 1852; *Schistosoma haematobium* (Bilharz) Weinland, 1858; *Gynaecophorus haematobius* (Bilharz) Diesing, 1858; *Bilharzia haematobia* (Bilharz) Cobbold, 1859; *Bilharzia capensis* Harley, 1864.

³ The position of the spine has given rise to considerable discussion, and the view has been advanced that the lateral spine may belong to a species (*S. mansoni*) of fluke which is distinct from that which produces the terminal spine. Clinical and geographic data also are advanced in support of this view. Against the newer interpretation are presented certain embryological facts.

⁴ SYNONYMS.—*Schistosomum japonicum* Katsurada, 1904, August 13; *Schistosoma cattoi* Blanchard, 1905.

The young worms live in the veins of the liver; in the portal vein there are but few young pairs; in the veins of the intestine and bladder wall, paired flukes are numerous. Oviposition begins while the parasites wander from the portal vein to the pelvis, and eggs are deposited in various organs. The eggs with lateral spine are especially common in the liver and intestine. The ova (80 by 30μ in utero) increase in size as they work through the tissues into the lumen of the intestine or of the bladder; during this process they (or at least in *S. haematobium*) develop a ciliated embryo so that the miracidium is present when the egg is voided in the urine. Upon coming into water this embryo escapes from the egg-shell and it may live in water for thirty to forty hours.

Source of Infection.—From the miracidium in water to the time that the parasites are found in the veins of the liver, the complete life-history is unknown but evidence is rapidly accumulating which points to an infection directly through the skin. In fact, infection experiments on cattle, dogs, and cats seem to prove definitely that the infection with *S. japonicum* actually does occur through the skin while the animals are standing or wading in infected water, and helminthologists are expecting that similar experiments with *S. haematobium* will give similar results. It is at least doubtful, however, whether we are justified at present in assuming that infection through infected drinking water is excluded. Some authors (Allen, Brock, Harley) assume direct infection through the urethra and anus.

Frequency.—Bilharziosis is much more common in males than in females and in rural districts than in cities. In a school near Cairo, Kautsky Bey found 98 cases in 124 boys examined, or nearly 80 per cent.; in two city schools, Engel Bey found 61 children, or 30.5 per cent. infected in 200 examined (Looss, 1905). Postmortem statistics indicate that it is present in quite one-half of the population of Egypt (Manson), and it is even more common in Uganda (Low). Several to 40 (Sonsino) or even to 300 (Kartulis) worms may be found in one patient. Ruffer (1910) reports the eggs from the kidneys of 2 out of 6 Egyptian mummies dating from 1250 to 1000 B.C.

Duration.—The incubation of the disease is about four to five months (Brock *et al.*), and it is said to last usually about two years (Milton, 1902); cases of longer duration are recorded in patients who have passed ova for nine (Sonsino) to fifteen years (Lortet) after leaving the infected area, and some authors refer to cases of twenty to thirty years' standing; evidence is not presented that these were not due to repeated infection.

Pathology.—It is generally admitted that it is the eggs rather than the worms that are of importance. These ova work their way into and through the tissues, particularly in the walls of the bladder, rectum, and vagina; they may also be found in the liver, lungs, heart, spleen, pancreas, kidneys, omentum, peritoneum, appendix, ligaments of the uterus, in gall-stones, and in the cutaneous epithelium. At first the eggs lie in the blood capillaries, but leaving these they collect in groups in the tissue, the infiltrated places appearing as yellowish to whitish specks, and as the lesion increases it forms a papular elevation containing eggs and minute dilated bloodvessels. These thickenings increase in size

and may coalesce until the entire mucous membrane of the bladder becomes involved. Round, slightly projecting, dense patches of inflammatory thickenings, with granular surface and of hard consistency are seen, especially in the trigonum. After a certain age the patches begin to break down, and even slough, giving rise to ulcers and crevices on their surfaces, which tend to retain a certain amount of urine and favor deposition of its salts. In some cases the increase in the mucous membrane seems to be out of all proportion to the development of fibrous tissue and, in these cases, polypoid excrescences, sometimes ulcerated, may protrude into the lumen and may contain the worms as well as their ova. The bilharzia growths may cause retention of urine, resulting in dilatation of the ureters and involvement of the kidneys. The muscularis hypertrophies. The capacity of the bladder is decreased and its mucosa becomes covered with a bloody mucus containing numerous eggs. Carcinoma may develop.

Lesions similar to those of the bladder may be found also on the prostate, in the ureters (especially the lower third), less frequently in the pelvis of the kidney. The ureters may present constrictions and spindle-shaped or sacculated dilatations. Pyelitis, hydronephrosis, abscess, etc., may follow, and calculi (more important in the early stages of the disease) may form in the bladder, ureters, or kidneys. The vesiculae seminales, vagina, and cervix may also show a hyperplasia with a bloody discharge containing fluke eggs. Rectal bilharziosis ranks second to the vesical form.

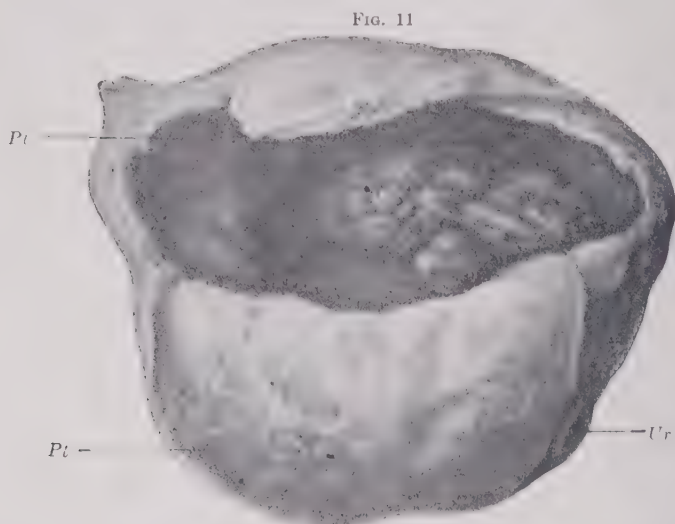
Symptoms.—*Course.*—Bilharziosis is rarely acute (Griesinger); it usually stretches over years and if death occurs, it is, as a rule, from some intercurrent disease; Ruffer isolated the colon bacillus in the kidney of all the fatal cases he observed (Innes).

Types.—There are two chief forms of the malady but they may occur together. If the ova are confined chiefly to the urogenital system the prominent symptoms are: hematuria; pains in the lumbar region, left iliac fossa, thigh, or vulva, either spontaneous or on micturition; cystitis, vesical calculus, urinary fistulae, vaginal tumors, and nephritis may develop. If the ova are confined chiefly to the rectum the most prominent symptoms are: bloody stools, diarrhoea, prolapse of the rectum and papilliform growths; thus far the Asiatic parasite has been reported only in connection with intestinal bilharziosis; the so-called *S. mansoni* also is supposed to be associated especially with the intestinal form of the disease.

Hematuria.—This is the earliest and most prominent symptom. In many cases the patient suffers little or no inconvenience. The simple hematuria occurs chiefly in the better classes, the severer forms of bilharziosis occurring among persons who are subject to long and severe physical labor and almost exclusively among men. At the end of micturition a few drops of more or less pure blood are expelled and this may be the only symptom observed; the amount of blood lost is usually small, but in some cases more extensive; it may clot in the bladder and cause acute retention. Later, vague pains in the perineum, lumbar region, over the pubes, and a burning sensation in the urethra during

micturition are experienced. At first the frequency of urination is not increased. All symptoms increase temporarily after excesses in diet or exercise, or during straining in defecation. The sediment of the urine contains blood cells, epithelium, mucus, and blood-fluke eggs.

The simple hematuria may be followed by *vesical catarrh*, increased micturition with severe pain and tenesmus, later by pronounced *cystitis*. The urine gradually loses its normal condition and becomes bloody, cloudy, and offensive; loosened tissue from the bladder may clog the urethra; residual urine becomes constant; pyelonephritis and septic cystitis may result. Relatively soft vesical *calculi* may form and in infected geographical areas cases of vesical calculi commonly give a history of hematuria. Calculi may also form in the kidneys or ureters and cause hydronephrosis. Hypertrophy, contraction or dilatation of



Bilharziosis of the bladder. *Ur*, urethra; *Pl*, flat, hard, encrusted elevations; note the cauliflower-like growth in the bladder. (Looss.)

the bladder may occur. Pressure on the bladder causes pain; constipation is reported as general, and defecation causes emission of a few drops of blood from the urethra. In some cases there may be involvement of the prostate or of the vesiculæ seminales, causing spermatorrhœa, and in the latter event ova are found in the seminal discharge.

Urinary *fistula* is a frequent complication. This may form at any point near the genitalia but especially in the perineum near the scrotum; or on the posterior surface of the scrotum, where the fistulæ are usually multiple, and when the openings are numerous (up to 50 are recorded) some of these may be on the penis, over the pubes, near the anus, on the legs, etc. According to Milton, all simple fistulæ spring from the urethra; most fistulæ take origin from the pubic side or roof of the urethra, a few from the perineal side or floor; most floor fistulæ are formed just in front of the bulb, but some may be found in the penile urethra.

Urethral stricture is also encountered, especially (Milton) in case of floor fistulae; the latter form from periurethral abscesses. The urethra may become solid so that the catheter cannot be passed.

As a result of the severer infections, the patient becomes anemic, debilitated and wasted, and may succumb to some intercurrent disease.

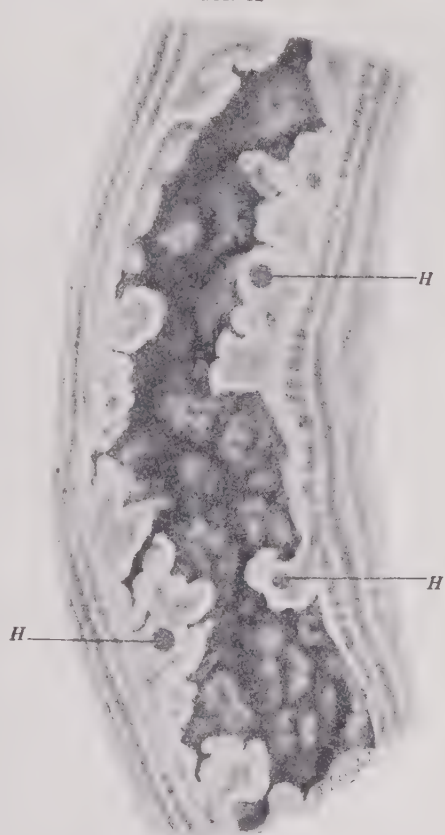
When bilharziosis occurs in women in Africa it is usually as a hematuria. In vaginal bilharziosis there is subacute vaginitis, the mucosa thickens (especially on the posterior surface of the vagina) and becomes hard and dry with longitudinal and transverse folds. Polypoid growths may be encountered, sometimes filling the entire vagina. The lesions may occur in the vagina without appearing in the bladder; bilharzia papilloma may be confused with epithelioma.

In rectal bilharziosis the mucous membrane becomes hypertrophied, excessively vascular, and of rich, red-velvet appearance; small or larger, simple or branching, soft, pile-like or coral-like growths are found from the sphincter up to the sigmoid flexure. There is excessive secretion of mucus and the patient feels as if his rectum were full and as if he wished to defecate. Little is passed, mixed with bloody mucus containing fluke-eggs. Repeated straining at stool causes prolapse of the rectum; at first this returns of itself but as time advances it must be helped back; finally the sphincter weakens and the rectum remains prolapsed; it becomes

septic and may cause death. "Wading fever," in China, with "giant urticaria" and "slight bloody movements," has recently been explained as due to *S. japonicum* (Logan, 1911). In connection with the endemic Asiatic infection Sambon (1908) mentions enlargement of liver and spleen, cachexia, ascites, cirrhosis. Lane (1910) reports a case of an English sailor operated for appendicitis; terminal spined *Schistosoma* eggs were found in the appendix and vesical bilharziosis was discovered; the infection took place in Africa.

Prognosis.—In case of light infection, the patient may not be inconvenienced. In simple uncomplicated cases, prognosis is not unfavorable but the possibility of new infection (since a careless patient is always a

FIG. 12



Bilharziosis of the rectum. H, cavities filled with blood. (Looss.)

danger to himself as a source of infection) and the liability to septic infection, make bilharziosis a serious disease (Looss). In general, the prognosis of vesical bilharziosis is practically that of chronic cystitis depending upon an irremediable but not in itself fatal cause.

Clinical Diagnosis.—This should be made by microscopic examination of the urine and feces to find the eggs of the parasites. These will be found especially in the last few drops forced out at the end of micturition; or in the last drops of urine in the catheter. In old cases, however, the eggs may not be present in the urine; if necessary, the surface of the bladder may be scratched and the shreds examined for eggs or the polypoid growths in the rectum may be removed and examined (Manson).

To distinguish concurrent affections note: Chyluria (chyle in the urine, a large clot with oil granules and globules, and *Filaria* will be found in the blood); calculus (be careful not to mistake the hard, sandy, raised portions of the bladder wall for stones); gonorrhœa (history); and enlarged prostate. Floor-fistulæ may be mistaken for stones in the urethra, but the sound passes through and, as it is withdrawn, pus follows. In the rectum, distinguish bilharziosis from piles; large bilharzian tumors may resemble epithelioma or sarcoma.

Blood.—Le Dantec (1904) gives the leukocyte count as: Polynuclears, 57 per cent.; mononuclears, 35 per cent.; eosinophiles, 8 per cent.

Death is due to exhaustion from pain and want of rest, together with debility consequent on the constant hemorrhage, aided by poisoning from absorption of septic matter from the intestine, or to pyonephrosis, pyemia, or uremia.

Treatment.—No radical specific medical treatment is known at present, some authors even claiming that such attempts are undesirable and that efforts must be confined to palliating the effects of the presence of the parasites. Good results are claimed by some authors from daily doses of male fern, santonin, quinine, or methylene blue (3 gr., t. i. d.), but the general opinion seems to be that treatment must be symptomatic for the cystitis and dysentery, and, further than that, operative if necessary. Milton warns against lithotomy if not absolutely necessary, but he has good results from lithotrity; in case of very extensive changes in the bladder he uses double perineal drainage, the drainage-tubes being retained eight to ten days, but he says that the results cannot be foreseen, as the growths slough and the patient is not likely to survive; it may, however, simply be a question between draining and allowing the patient to suffer. Perineal fistulæ are treated on general surgical principles.

Hyperplasia in the vagina and cervix is treated by excision of thickened and infiltrated mucous membrane.

In rectal bilharziosis the irritation is allayed by local sedatives and astringent applications. The rectal tumors are removed so far as possible. In case of high tumors Milton destroys them by swabbing for about a minute with chloride of zinc solution 1 to 10, then drying out the excess with cotton followed by washing with copious salt solution.

Operation on the prolapsed rectum, avoiding the sphincter, is more or less successful in fresh cases, but not in advanced cases. It is often difficult to decide whether excision of the prolapsed portion is justifiable.

Prevention.—Until the life-cycle and source of infection are better understood the best method of prevention cannot be definitely stated in detail but it is probably one or both of the following and for the present both should be carried out: (1) Guard water against contamination with urine from bilharzia patients; water so guarded for two days may be safely used for bathing purposes (Looss); (2) drink only filtered or boiled water when in an infected district.

OPHTHALMIC DISTOMATOSIS

Ophthalmic distomatosis has been reported for man on only two occasions: *Monostomulum lentis* (Gescheidt, 1833) is a trematode of uncertain systematic position which has been reported once, in Odessa, in the crystalline lens. Possibly it is an erratic liver-fluke. *Agamodistomum ophthalmobium* (Diesing, 1850) is also of doubtful systematic position (possibly an erratic liver-fluke). It is reported once, in Dresden, between the crystalline lens and its capsule.

TENIASIS—CESTODE INFECTION

Terminology.—*Taenia* was the original cestode genus (1758) and has served as the great collective genus of the tapeworms. It is now confined to cestodes of the type of *Taenia solium*, but the term teniasis may be conveniently retained to denote any cestode infection. We may have two kinds of teniasis: namely, (a) intestinal infection with the tapeworm stage, or (b) somatic infection with the larval stage. In some animals adult tapeworms are found in the gall ducts.

INTESTINAL TENIASIS—TAPEWORM¹ INFECTION

The day is passed when a simple diagnosis of "tapeworm" is sufficient, for it may be a matter of importance, both to the physician and the patient, to establish what particular kind of tapeworm is present. Upon such determination may rest the question of the time of treatment, the precautions to be taken, and even—in exceptional cases—the risks to be run and the chances for complete recovery.

So far as is established, man seems to be the normal and sole host for the sexual stage of at least two of the large tapeworms, *Taenia saginata* and *T. solium*. Man, together with the dog, probably forms the normal host for a third large tapeworm (*Dibothriocephalus latus*). In common with rats and mice, man seems to have become a normal host for the dwarf tapeworm (*Hymenolepis nana*) although it seems

¹ For keys to and specific diagnoses and full synonymy of the various tapeworms of man see Stiles, 1906*a*, pp. 1 to 104, Figs. 1 to 160. *Bulletin* 25, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington. For detailed index to subject, see *Bulletin* 85, Hygienic Laboratory, etc.

probable that the worm in man is not exactly identical with that of the rodents; in fact, strong indications are not lacking that the worm (*H. n. fraterna*) in rats and mice is at least varietally, perhaps specifically, distinct from the worm in man.

Occasionally, though rarely, as accidental host, man harbors the double-pored tapeworm (*Dipylidium caninum*) of dogs and cats, the flavopunctate tapeworm (*Hymenolepis diminuta*) of rats, and the lanceolate tapeworm (*H. lanceolata*) of ducks and geese. The other tapeworms reported for man are: *Taenia confusa* (twice in the United States), *T. philippina* (once in Manila), *T. brenneri* (once in Nigeria), *T. hominis* (once in Aschabad), *T. africana* (two specimens from East Africa), *Davainea madagascariensis* (occasionally in the tropics), *D. asiatica* (once in Asiatic Russia), *Bertiella satyri* *Dibothriocephalus cordatus* (Greenland), *Dib. parvus* (once in Tasmania or Syria), *Diplogonoporus grandis* (twice in Japan) *Dip. brauni* (once in Rumania), *Braunia jassyensis* (once in Jassy); but too little at present is known of the occurrence of these species to permit a definite judgment as to whether man is their normal or simply an accidental host, except perhaps in the case of *Dib. cordatus* and *Bertiella satyri*, for which man seems to be an accidental host. Interesting as the sixteen last-named infections are, it may be said that from a clinical point of view our present knowledge of the adult tapeworms in man is based chiefly upon three large species (*Dib. latus*, *Taenia solium*, *T. saginata*) and one small species (*H. nana*). Of these the average practitioner in Australia, England, and North America will come in contact especially with the fat tapeworm (*T. saginata*); he will doubtless meet infections with the dwarf tapeworm (*H. nana*), but will usually fail to recognize them, although in some parts of the United States he will probably have five or more cases of this parasite to one of the fat tapeworm; it is the exception that the pork-measle or armed tapeworm (*T. solium*) is found; while probably not one physician in a hundred in Australia, England, and North America has seen an infection with the broad tapeworm (*D. latus*), and if he does see such, it may be chiefly imported cases among Russians, Swedes, Finns, Germans, or in persons who have visited the more infected European or Asiatic localities; the broad tapeworm seems now likely, however, to become endemic in the northern lake region of the United States.

All four of these species present certain points which should be borne in mind. The pork-measle tapeworm, though not common, is by far the most dangerous. The dwarf tapeworm is the most common in some localities, though its frequency in others is not established; although it is very small it may occur in large numbers and produce severe symptoms. The fat tapeworm is the most common of the larger forms; it may produce severe symptoms, is sometimes difficult to expel, but is not dangerous as compared with *T. solium*. The broad tapeworm may be associated with a more or less severe anemia.

The Fat Tapeworm.—*Taenia* (*Taeniarhynchus*) *saginata* Goeze, 1782.—

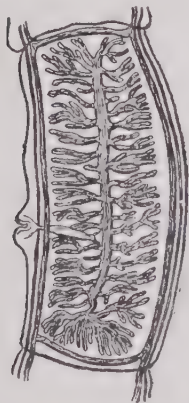
Geographical Distribution.—Practically cosmopolitan.

Zoölogical Distribution.—The adult is known only for man. The larva (*Oysticerus bovis*) is found in cattle; it is also reported by several

authors for man but doubts arise regarding the determinations; experiments to grow it in apes, dogs, goats, hogs, rabbits, and sheep have been negative, but it is reported that Heller succeeded in infecting a sheep, and that Zenker and Heller were able to infect young goats.

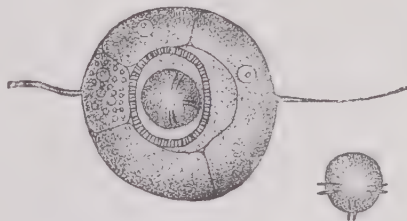
The Parasite.—The fat or unarmed tapeworm, *Taenia* (*Taeniarhynchus*)¹ *saginata*,² is one of the largest known cestodes, attaining a length of about 4 to 8 or 10 meters; the head is without hooks; there may be more than a thousand segments present; only two ovaries are found in

FIG. 13



Gravid segment of beef-meat tapeworm (*Taenia saginata*), showing lateral branches of the uterus, enlarged. (Stiles.)

FIG. 14



Egg of beef-meat tapeworm (*Taenia saginata*) with thick egg shell (embryophore), containing the six-hooked embryo (onchosphere), enlarged. (Leuckart.)

each mature segment; the uterus in the gravid segments has 15 to 35 slender dichotomous lateral branches each side of, and shorter than, the median stem; genital pores lateral (marginal), irregularly alternate; terminal segments attain 16 to 25 mm. long by 4 to 7 mm. broad; eggs with thick, dark, radially striated embryophore ("inner shell," or "shell" in most medical works), 30 to 40 by 20 to 30 μ .

Source of Infection.—This parasite is obtained through eating beef, especially the tongue and the muscles of mastication, infected with *Cysticercus bovis*.³ Cattle become infected by swallowing the embryo

¹ In zoölogical writings, a capitalized name inserted in parentheses between the generic and the specific names denotes the subgenus. The present genus, *Taenia*, for instance, may be divided into the subgenera: *Taenia*, type *T. solium*; *Taeniarhynchus*, type *T. saginata*; and *Multiceps* Goeze, 1782 (*Coenurus*, 1808) type *T. coenurus*. Subgenera are used in zoölogy for several purposes: Their chief use is to enable the classification of species into groups to which generic rank is not given; another use of subgenera is to foreshadow probable changes in the classification. When a genus is divided into subgenera, it is not necessary to cite the subgeneric name when referring to the species. Thus, *Taenia saginata* is as valid a citation as *Taenia* (*Taeniarhynchus*) *saginata*.

² SYNONYMS.—*Taenia solium* Linnaeus, 1758 pro parte; *T. mediocanellata hominis*, seu *T. mediocanellata* seu *T. zittaviensis* Küchenmeister, 1852; *T. inermis* Moquin-Tandon, 1860.

³ SYNONYMS.—*Cysticercus taeniae saginatae* Leuckart; *C. bovis* Cobbold, 1866; *C. taeniae mediocanellatae* Knoch, 1868; *C. inermis* of various Germans and others.

onchosphere), encased in its embryophore, in their food or in water contaminated directly or indirectly with infected human feces. Ransom has recently traced an unusually interesting instance of the infection of a number of cattle because of the poor drainage from soil-polluted ground.

Frequency.—This is the most common of the large tapeworms of man in North America and Europe (except in certain regions where *Dibothriocephalus latus* abounds), but it will doubtless gradually decrease in frequency because of the meat inspection and cold storage of beef. It is reported as exceedingly common in certain localities of Africa and Asia. It is more common in females than in males, and while it may be present in patients of almost any age, it is more common in people between twenty and forty. Usually only one specimen is present in a patient, but infections with from 1 to 59 worms are reported.

Duration.—Beyond the fact that persons may harbor this worm for a number of years, the exact longevity of this species is not established; considering the method by which the segments are formed, the age of the worm seems to be, theoretically, potentially almost indefinite.

Special Medical Features.—The fat tapeworm is not only more common than *T. solium*, but the general consensus of opinion seems to be that it is more difficult to expel, despite the absence of hooks from the head. While clinical reports seem to show that anemia is more likely to result from *T. saginata* than from *T. solium*, and less likely than from *D. latus*, the fat tapeworm is really of much less importance than *T. solium*, for it does not combine with it the danger of cysticercosis which we may find associated with infection with *T. solium*. Hence, if treatment for *T. saginata* is not convenient at the time of diagnosis (as in case of pregnancy) this can be postponed without any special danger.

Differential Diagnosis.—In general it is unwise for the physician to trust to distinguishing *T. saginata* from *T. solium* on the microscopic examination of the eggs found in the feces. The author has examined the adult worms which various persons have positively determined by this method as being *T. solium* and in every case thus far the parasite has proved to be *T. saginata*. It is also unwise to rely only upon the form of the segments. A safer plan is to press the discharged segments between two pieces of glass, hold the preparation to the light, and count the lateral branches of the uterus. If the head is found, determine the presence (*T. solium*) or absence (*T. saginata*) of hooks.

Prevention.—Proper disposal of human feces should prevent the infection of cattle; a proper system of meat inspection¹ prevents the infection of man; the cysticerci in beef die within three weeks after the death of the steer, so that beef which has been killed for twenty-one days will not transmit this parasite; thorough cooking or thorough salting of the meat also kills the parasite.

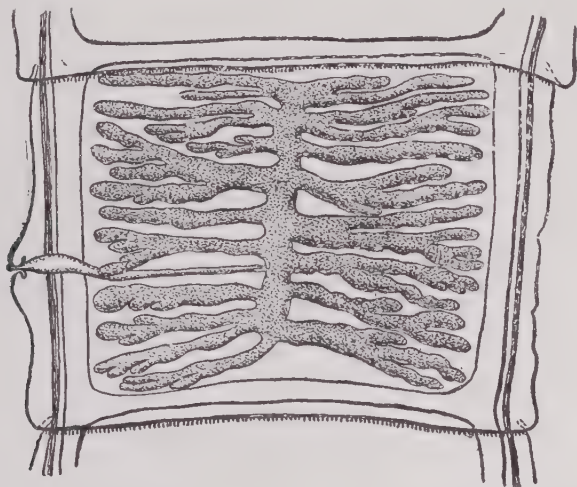
Taenia (Taeniarhynchus) africana Linstow, 1900, is a species closely allied to *T. saginata*; only two specimens have been found—in the negro in German East Africa. The parasite attains 1.4 meters in length; scolex unarmed; segments about 600 in number, always broader than

¹ See Stiles, 1898 a, pp. 77 to 83. *Bulletin* 19, U. S. Bureau of Animal Industry.

long, attaining 7 mm. in length by 12 to 15 mm. in breadth; uterus with 15 to 24 simple (not dichotomous) branches each side of, and longer than, the median stem; embryophore 31 to 39 by 33.8μ . The life-cycle and source of infection are unknown but the zebu has fallen under suspicion as possibly representing the intermediate host.

Taenia (Taeniarhynchus) hominis Linstow, 1902, was found once, in Aschabad, in a girl. The parasite measured 70 mm. long by 1.11 to 1.97 mm. broad. The scolex possesses a rudimentary rostellum without hooks; suckers directed postero-anteriorly; caudad of suckers a circular ridge is present. The genital organs were not developed, but von Linstow considers that the indications are that this worm may attain as great size as *T. saginata*.

FIG. 15



Gravid segment of pork-measle tapeworm (*T. solium*), showing the lateral branches of the uterus, enlarged. (Stiles.)

The Pork-measly Tapeworm.—*Taenia (Taenia) solium*.—**Geographical Distribution.**—Practically cosmopolitan, following the hog.

Zoological Distribution.—Adult known only for man; experiments to grow it in a monkey (*Macacus cynomolgus*) and in dogs, guinea-pigs, hogs and rabbits have been negative. The larva (*Cysticercus cellulosae*¹) is found especially in hogs; it is said that it may, occasionally, occur in sheep, but Ransom's investigations raise a question as to the correctness of the zoological determination; it is also said that it will develop in young dogs.

The Parasite.—The armed or pork-measle tapeworm, *Taenia (Taenia) solium*² (Linnaeus, 1758), is slightly smaller than the fat tapeworm; it does not usually measure over 2 to 3.5, 6 or 8 meters in length; the head is armed with a rostellum, bearing a double row of hooks, of larger and smaller size, 22 to 32 in number; genital pores lateral (marginal),

¹ SYNONYMS.—*T. cellulosae* Gmelin, 1790; *C. cellulosae* (Gmelin) Rudolphi, 1808.

² SYNONYMS.—*T. solium* Linnaeus, 1758 (after elimination of *T. saginata* and *T. hydatigena*)

irregularly alternate; mature segments contain 3 ovaries, due to the fact that the ovary on the pore-side of the segment is divided; the segments may attain 10 to 12 mm. in length by 5 to 6 mm. in breadth; 800 to 900 segments may be present; in gravid segments, the median uterine stem possesses 7 to 15 lateral dichotomous branches each side; "eggs" (embryophore) very similar to those of *T. saginata*, 31 to 36 μ in diameter.

Source of Infection.—This parasite is obtained by eating undercooked, or underpickled, or undercured pork or wild boar meat. The hogs become infected by eating human feces containing the egg with its enclosed embryo, or from food or drink contaminated with these eggs. To build a privy over the pigpen, as is done in rural districts, means the formation of an endless chain in the biology of this worm.

FIG. 16



Section of a tongue heavily infested with measles, natural size. (Stiles.)

Frequency.—As has been shown by Leidy, Osler, and the writer, this is not a very common parasite in the United States and Canada, despite the statements of several authors to the contrary. Of 300 tapeworms from man examined by the author from 1891 to 1895, 297 were *T. saginata* and none *T. solium*. Of 28 tapeworms recently (1905) examined by him in two New England museums, 23 were *T. saginata* (several were labelled *T. solium*), 4 were *D. latus*, and 1 was too poor to determine. From 1891 to 1905 the only authentic specimen of *T. solium* sent to the writer came from Germany. Osler reports 76 cases of the cysticercus in hogs out of 1000 examined in Montreal; and the writer has seen several American cases of cysticercosis in hogs and man due to this species; there can be no doubt regarding its occurrence in this country. Perfectly authentic cases of *T. solium* in man have been recognized in the United States. *T. solium* is said to be rather common in Panama. The relative infrequency of the pork tapeworm in America is due probably to (a) national culinary habits, (b) the curing methods, and (c) the federal

meat inspection. In Europe, *T. solium* is decreasing in frequency, because of the meat inspection. It is not found among orthodox Jews, or among other people who do not eat pork. It is especially likely to be found in people who eat raw or rare pork. It may be found in patients of almost any age, but appears to be more common in people between twenty and forty years.

Duration.—The longevity of the individual adult parasite is not definitely established, but it can doubtless live for years (ten to fifteen or more).

Special Medical Features.—While less likely, according to clinical reports, to result in anemia than is either *T. saginata* or *D. latus*, the fact must constantly be held in mind that *T. solium* is dangerous especially because of the possibility of its producing cysticercosis (see page 263). On account of this danger, it is much more important to treat promptly the infection with *T. solium* than the infection with any other tapeworm. Further, not only is a patient with *T. solium* a constant danger to himself, but also to other members of his family, and especially to anyone occupying the same bed with him. Accordingly, a patient with *T. solium* should never sleep in bed with another person, not only between the time of diagnosis and treatment, but also until a definite cure is established. He should also be warned to be unusually cautious about his personal habits, relative to washing his hands and cleaning his finger nails.

Prevention. — Feces from infected patients should be so disposed of that they cannot infect hogs; hogs heavily

FIG. 17



Gravid segment of *T. confusa*, to show the uterus. $\times 6$. (Guyer.)

FIG. 18



Onchosphere of same surrounded by embryophore, from uterus. $\times 660$. (Guyer.)

infected (severe hog-measles, acute cestode tuberculosis) should be destroyed, but if the infection is very light no valid hygienic objection can be raised against eating the meat *in case it is thoroughly cooked*; cold-storage is not so effective against this parasite as it is against *Cysticercus bovis*, for *C. cellulosae* has been found alive twenty-nine days after its host was slaughtered.

Taenia (Taenia) teniaeformis (Bloch, 1780) is a tapeworm which cats contract from eating mice containing *Cysticercus fasciolaris*. Krabbe thinks its occasional presence in man is possible, because in Jutland, hashed raw mice are occasionally eaten as a remedy for retention of urine. No authentic case of such infection seems to be reported.

Taenia (Taenia) pisiformis (Bloch, 1780) is a tapeworm which dogs contract by eating rabbits infected with *Cysticercus pisiformis*. Vital (1874) reports this tapeworm in man, but legitimate doubts may arise regarding the correctness of the zoölogical determination, especially in view of the fact that Galli-Valerio (1898) was unable to infect himself with this species experimentally by swallowing the larval stage.

Taenia (Subg.?) confusa Ward, 1896, has been found in Lincoln, Nebraska. It attains 5 to 8 meters in length; head unknown; segments may attain 27 to 35 mm. long by 3.5 to 5 mm. broad, greatest breadth 8 to 10 mm.; ovaries 2, distinctly reniform; uterus with 14 to 18 short, thick, dichotomous lateral branches each side of median stem; eggs 39 by 30 μ . Thus far little is known regarding the history and clinical significance of this American tapeworm, which should be looked for especially in the Northwest.

The Dwarf Tapeworm.—*Hymenolepis Nana*.—**Geographical Distribution.**—In North America this parasite has been found from Pennsylvania to Texas, but its distribution is probably much more extensive. It is also reported for South America, Europe, Asia, Africa, and is probably more or less cosmopolitan.

Zoölogical Distribution.—Several authors (Grassi, Lutz, Ransom, and others) consider *H. nana fraterna*¹ Stiles, 1906, of rats and mice identical² with *H. nana* of man, but other authors (Moniez, Braun, Looss) are inclined to doubt this identity. Grassi, Looss, and the writer were unable to transmit the parasite of man to rats.

The Parasite.—*H. nana*³ (Siebold, 1852) is the smallest tapeworm known for man. It measures 5 to 45 mm. long by 0.5 to 0.9 mm. in maximum breadth, and is composed of 100 to 200 small segments. The rostellum is armed; there are 3 testes to each segment, and the genital pores are unilateral. The eggs have 2 distinct membranes: outer membrane 30 to 60 μ in diameter; inner membrane 16 to 34 μ ,

¹ *H. murina* (Dujardin, 1845).

² From the hygienic point of view this assumption must be made until the zoölogical points in question are definitely settled; applied zoölogy is of course dependent upon theoretical zoölogy, but in doubtful cases we must be more conservative in applied than in abstract science. The writer considers the form from rodents entitled to at least subspecific rank.

³ SYNONYMS.—(?) *Taenia murina* Dujardin, 1845 (not *T. murina* Gmelin, 1790); *Cysticercus fasciolaris* Rudolphi; *T. nana* Siebold, 1852 (not Van Beneden, 1858); *Hymenolepis nana* (Siebold) Blanchard, 1891; *H. murina* (Dujardin) Blanchard 1891; "*Hymenolepsis*" *nana* of Osler, 1895, and other authors (misprint).

presenting at each pole a more or less conspicuous mammillate projection provided with filamentous appendages. The adults are found especially in the upper two-thirds or three-fourths of the ileum.

Source of Infection.—*H. nana fraterna* develops in rats without any intermediate host; the eggs escape in the feces, and when swallowed, the onchosphere (embryo) bores into the villi of the intestine, where it develops within a few days into a larva (cercocystis); the latter reaches the lumen of the intestine and develops into the adult strobila. If the form in rats is identical with *H. nana*, man probably receives his infection from food soiled by the excrements of rats and mice. The large number of specimens sometimes found in man would at least indicate that *H. nana* probably develops in the manner described for the form that occurs in rats; auto-infection seems highly probable.

Frequency.—This parasite¹ is unquestionably much more common than is generally supposed, and indications are not lacking that, in certain parts of the world, at least, it is the most common tapeworm of man. The author found it in 4 cases (2.5 per cent.) of about 160 persons examined between Richmond, Va., and Florida; his assistants found it in 6 cases (4.8 per cent.) of 123 children in a Washington orphanage. It is rather common in children coming to the U. S. Marine Hospital in Wilmington, N. C., and examinations by the Southern State Boards of Health show that it is widely distributed in this area. Calandruccio estimates that in Sicily 10 per cent. of the children are infected. In Germany the parasite does not appear to be common. It has been found in patients from under five to over fifty years of age, but is more common in children from five to ten years old, and in boys than in girls. Crowded conditions, as in dormitories of orphan asylums, seem to be favorable to the spread of the parasite, which is, further, more common in poorer than in well-to-do families. From one or two to several thousand worms may be found in a patient.

Duration.—The length of life of the individual parasite is not definitely established, but infections have been reported as lasting from two months to two and one-half years.

Special Medical Significance.—Although this is a small tapeworm it seems a serious error to assume that it is of no significance. Light infections do not appear, *per se*, to be of much symptomatic importance, but they may lead to heavy infections productive of pronounced symptoms. The local lesions produced by the parasite seem to be slight, and Mingazzini suggests that the symptoms are due to a toxin eliminated by the worm.

Treatment.—Until recently male fern was reported as the only remedy which had been useful in expelling this worm, while cusso, kamala, santonin, thymol, and pomegranate were reported as having failed in the cases in which these drugs were tried. The writer has recently had fairly good results with the thymol treatment.

¹ For a complete discussion, in English, of the three species of *Hymenolepis* which occur in man, together with summary of cases, see Ransom, 1904 *d.*, pp. 1 to 138, Figs. 1 to 130. *Bulletin* 18, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington.

Prevention.—On the assumption that *H. nana* in man is specifically identical with the small tapeworm of rats and mice, the most important point in prevention lies in protecting food from these rodents. If a person is found to be infected, he should occupy a separate bed until fully cured.

Hymenolepis diminuta¹ (Rudolphi, 1819), the flavopunctate tapeworm of rats, occasionally occurs in man. It measures 10 to 60 mm. long by 2.5 to 4 mm. in maximum breadth, and is composed of 800 to 1300 segments. The head is unarmed; 3 testicles are present in each segment, and the genital pores are unilateral. The eggs are round to oval; the outer membrane (56 to 80 μ) may be radially striated; the inner membrane measures 24 to 40 by 20 to 36 μ . The larval stage lives in insects, such as the larva and adult of meal moths, earwigs and in adult beetles. Cases are reported for man, for the United States, South America, and Europe. The writer knows of several unpublished North American cases observed within the past five years.

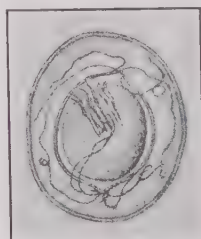
FIG. 19



Head and strobila of dwarf tapeworm. (*Hymenolepis nana*), enlarged. (Leuckart.)

Hymenolepis lanceolata² (Bloch, 1782), the lanceolate tapeworm of ducks and geese, has been reported once (in Germany) for man. This worm is supposed to pass its larval stage in small crustaceans belonging to the family *Cyclopidae*.

FIG. 20



Egg of *Hymenolepis nana* as seen in fresh feces, enlarged. (Ransom, from Stiles.)

Davainea madagascariensis (Davaine 1869) is known only for man, and has been reported 10 or 12 times (Comoro Islands, Mauritius, Siam, Nossi-Be, British Guiana, Philippines), chiefly in children. It measures 25 to 30 cm. long and is composed of 500 to 600 segments which

¹ SYNONYMS.—*Taenia diminuta* Rudolphi, 1819; *Hymenolepis flavopunctata* Weinland, 1858; *H. diminuta* (Rudolphi, 1819) Blanchard, 1891; "*Hymenolepsis*" *flavopunctata* of Osler, 1895, and other authors (misprint).

² SYNONYMS.—*T. lanceolata* Bloch, 1872; *H. (Dilepis) lanceolata* (Bloch, 1782) Weinland, 1858.

attain 2 mm. long by 1.4 mm. broad; head with large round suckers, rostellum with 90 hooks; genital pores unilateral; calcareous corpuscles present; about 50 testicles present; eggs with 2 clear shells, the outer possessing 2 mammillate projections; eggs collect in 300 or 400 egg-balls. The intermediate host is unknown, but Blanchard has suggested that possibly the cockroach (*Blatta orientalis*) plays this role.

FIG. 21

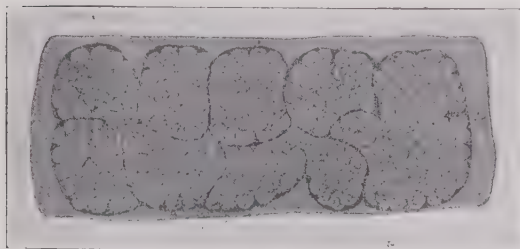
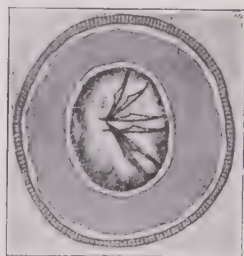
Gravid segment of *H. diminuta*, enlarged. (Grassi.)

FIG. 22

Egg of *H. diminuta* from man, greatly enlarged. (Bizzozero.)

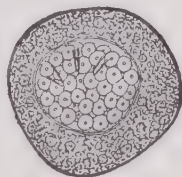
Davainea asiatica (Linstow, 1901) was found once in Aschabad, Asiatic Russia. The scolex is unknown, but the anatomy of the fragment indicates that the worm is a *Davainea*; it measures 298 mm. long by 0.16 to 0.99 mm. broad and possesses about 750 segments; calcareous corpuscles absent; genital pores unilateral; ventral canals very large; all genital organs are developed at 70 mm. from anterior end. The eggs collect in 68 to 70 egg-balls.

Dipylidium caninum¹ (Linnaeus, 1758), the double-pored dog tapeworm, has been reported for man (chiefly children), about 75 times, at least 2 of the cases being recorded in American literature. It measures 15 to 30 cm. in length by 1.5 to 3 mm. in maximum breadth. The head is armed with hooks and there are 2 sets of genital organs to each segment. It is a very common parasite in dogs, and the larval stage lives in dog lice (*Trichodectes canis*), the dog flea (*Ctenocephalus canis*) and the human flea (*Pulex irritans*). A very similar parasite occurs in cats.

Bertiella satyri (R. Blanchard, 891) is a tapeworm of the orang-outang which has been reported once as having been expelled by a young girl.

The Broad Tapeworm.—*Dibothriocephalus latus*.—**Geographical Distribution.**—This parasite is more common in the vicinity of large bodies of water (as in lake regions) than in regions of other topography. It is reported as especially common in Europe for the Russian Baltic provinces, Finland, Sweden, Denmark, Northeast

FIG. 23

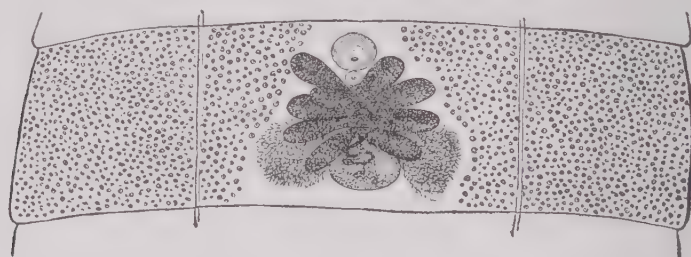
Egg of *Dipylidium caninum*. Note the six hooks in the embryo, greatly enlarged. (Stiles.)

¹ SYNONYMS.—*Taenia canina* Linnaeus, 1758; *T. moniliformis* Pallas, 1781; *T. cucumerina* Bloch, 1782; *T. elliptica* Batsch, 1786; *T. (Dipylidium) cucumerina* of Leuckart, 1863.

Prussia, Switzerland, and Northern Italy, but it occurs also elsewhere, as in Belgium, Holland, Ireland, Northern France, etc. It is common in Japan and Turkestan, and is reported for Iceland, N'gami Lakes (Africa), Madagascar, South Africa, and the United States. It bids fair to become almost cosmopolitan, following the fresh-water fish diet, and the Lake region of North America will probably soon consider this as an established endemic parasite; in fact, it may almost be considered endemic there at present.

Zoölogical Distribution.—The adult worm occurs in man, cats, dogs, and foxes (rare). The larval stage (a "plerocercoid") attains a length of 30 mm. and is found in the muscles and various organs of fresh-water fish, particularly in the pike, ling, or burbot, perch, and several members of the salmon family.

FIG. 24



Gravid segment of *D. latus*, showing the rosette uterus in the median line. $\times 6$. (Leuckart.)

The Parasite.—*Dibothriocephalus latus*¹ (Linnaeus, 1758) attains 2 to 9 or 10 meters in length by 20 mm. in maximum breadth; it is usually grayish yellow to brown in color, and composed of 3000 to 4200 segments, which are usually broader than long, especially in the anterior two-thirds of the strobila; posterior segments become quadrate or even longer than broad, and are especially characterized by the rosette spot (uterus) in the centre; genital pores ventromedian; eggs 68 to 71 by 45μ , with distinct operculum; laid during segmentation.

Source of Infection.—This tapeworm is contracted by eating raw or underdone fish.

Frequency.—Over 30 cases of infection with this parasite have been recognized for the United States, chiefly among foreigners. In some parts of Europe it is reported as the most common tapeworm of man, the frequency varying from 0.8 to 10, 20 and, locally, even to more than 50 per cent. of the population. In Turkestan and Japan it is the most common tapeworm of man. Very probably it will become more commonly known in the United States, for now that special attention has been directed to it, it will be more frequently recognized, and further, it is highly probable that immigrants have infected the fish of some of our

¹ SYNONYMS.—*Taenia lata* Linnaeus, 1758; *T. vulgaris* Linnaeus, 1758; *Bothriocephalus latus* (Linnaeus) Bremser, 1819; *Dibothrium latum* (Linnaeus) Diesing, 1850; *Bothriocephalus cristatus* Davaine, 1873; *Dibothriocephalus latus* (Linnaeus) Luehe, 1899.

lake regions. It is observed more commonly in adults but may develop in persons of any age.

Duration.—The growth, after infection, is very rapid. According to Braun, the average daily increase for the first five weeks is 31 to 32 segments, involving 8 to 9 cm. increase in length; Zschokke found the average daily increase in length to be 5.2 to 8.2 cm.; eggs may appear in feces twenty-four days after infection. Cases have been recorded of fourteen years' duration (Mosler).

Special Medical Significance.—This consists in the tendency to development of a severe anemia (Reyher, 1886, etc.) resembling pernicious anemia. Retinal hemorrhages have been reported in 50 per cent. of certain cases studied. This anemia is attributed by most authors to a toxin, supposed to be eliminated by the parasite, and a lethality as high as 16 per cent. has been reported by one author. Schauman (1894) found the red corpuscles reduced to an average of 1,311,000 (in males) and 1,273,000 (in females) in 38 out of 72 cases; he also found elevated temperature (99° to 104° F.) in 81 per cent. of his cases; the pulse is usually full, often accelerated to 90 or 120.

FIG. 25

Egg of *D. latus*. $\times 400$. (Looss.)

FIG. 26

An egg of *D. grandis* taken from the uterus.
 $\times 440$. (Ijima and Kurimoto.)

Clinical Diagnosis.—There should be little or no difficulty in diagnosing cases of this infection. As the uterus has a special uterine pore, eggs are constantly discharged from gravid segments and may be found in the feces. The segments show a tendency to be passed in small chains and ought not to be confused with those of the other tapeworms.

Prevention.—Feces of persons harboring this worm should be cared for in such a way that the eggs contained therein do not gain access to fresh-water streams or lakes. Thorough cooking of fish will protect man from infection.

Ward (1906) has reported, but not described, a new bothriocephalid tapeworm as occurring in the United States.

Dibothriocephalus cordatus¹ (Leuckart, 1863) is reported in Greenland for man, dogs, bearded seal, and walrus. Its reported introduction into the vicinity of Dorpat and Berlin (Prussia) is based upon an error of zoölogical determination. It measures 80 to 115 cm. long with a maximum breadth of 7 to 8 mm. and is composed of about 600 segments;

¹ SYNONYM.—*Bothriocephalus cordatus* Leuckart, 1863.

uterus with 6 to 8 lateral loops each side; the head is heart-shaped; neck absent; eggs 75 to 80 by 50 μ . It is probably contracted by eating fish.

Diplogonoporus grandis (Blanchard 1894) has been found twice in Japan. It may attain 10 meters in length, by 25 mm. in maximum breadth. It is similar to *Dibothriocephalus*, but with 2 complete sets of genital organs to each segment. The eggs are brownish, rather opaque, 63 by 48 to 50 μ . The source has not been demonstrated but infection probably takes place through eating fish.

Ashford, King and Gutierrez (1904, p. 92) report 1 case of this infection in Porto Rico but as the determination was made solely upon the eggs in the stools while the adult parasite was not seen, legitimate doubts arise regarding the correctness of the zoölogical determination.

Symptoms.—Irregular appetite with occasional pains extending from the region of the stomach to the back; intestinal disturbance indicated by diarrhœa, colic, and constipation; anemia; poorly nourished condition, weakness, and inclination to faint.¹

Diplogonoporus brauni (Leon, 1908) has been recorded once in Rumania. It measures up to 29 cm. long, scolex 1 mm., bothria narrow, neck absent, segmentation indistinct, segments short and up to 6 mm. broad.

Braunia jassyensis (Leon, 1908) has been reported once, in Rumania. It measures up to 18 cm. long by 12 mm. broad, scolex triangular, bothria small, neck absent, external segmentation indistinct, a dorsal and a ventral median longitudinal groove present.

General Symptoms of Intestinal Taeniasis.—In connection with the various species of tapeworm found in man, reference has been made to the special medical significance of each form. In regard to the general clinical picture presented by patients harboring tapeworms, one noted clinician has remarked that its chief characteristic is its lack of anything characteristic. That a person may harbor a tapeworm, especially one of the smaller species, and be unaware of the fact, cannot be doubted; and this fact has led more than one person to minimize the importance of cestode infection. On the other hand, that tapeworm infection may result in severe symptoms is equally well established, for in numerous cases such symptoms have disappeared with the expulsion of the parasite; and this fact has led some observers to exaggerate its importance. We shall probably follow a justified mean between these extremes if we consider that the severity of the symptoms varies with the species of tapeworm present, with the number of the parasites, and with the age and general physical and nervous condition of the infected person. The injury is attributed to the following factors in particular: mechanical obstruction, injury, or irritation to the intestinal mucosa, loss of food which goes to the parasite instead of to the host, and toxins produced by the worms or by the disintegration of segments.

The appetite varies; it may be decreased, increased to a point of insatiability or the two conditions may alternate; Hirsch reports loss of appetite in 6 per cent. of cases, bulimia in 10 per cent., capricious appetite

¹ For an account of this worm, in English, see Stiles and Taylor, 1902 *a*, pp. 43 to 47, Figs. 22 to 28. *Bulletin* 29, U. S. Bureau Animal Industry.

in other cases.¹ Seeger records irregular appetite or bulimia in 31 per cent. (selected cases).

Salivation is often mentioned; Hirsch records it for 6 per cent. Erucation finds frequent mention; Hirsch reports it for 5 per cent. Nausea is common; Hirsch reports it in 13 per cent.; Seeger reports frequent nausea, with vomiting or feeling of faintness in 49 per cent. Vomiting may occur, and in some instances the tapeworm or portions of it have been vomited; this is particularly dangerous if the worm is *T. solium*.

Abdominal pains are very commonly complained of: they may be of the nature of colic or of gastralgia; they are referred to different parts of the abdomen, are of varying severity, sometimes intermittent; there may be borborygmi, a sense of distortion or twisting in the bowels, or a sensation of a ball or weight rolling around in the abdomen following the movements of the body. In experimental infection on myself the most pronounced and common symptom was that peculiar sensation one often has upon the sudden descent of an elevator; this occurred particularly while walking. Huber, in experiments upon himself, experienced a gnawing sensation in the epigastrium. Seeger reports abdominal pains of various sorts in 42 per cent., and peculiar sensations of movements in the abdomen in 16 per cent., acute colic, 17 per cent.; Hirsch reports abdominal pains as common, colic in 14 per cent. Digestive troubles are reported by nearly all authors. Constipation (5 per cent., Hirsch), diarrhoea (6 per cent., Hirsch), or irregularity of bowels (3 per cent., Hirsch) may obtain. Seeger reports digestive troubles and irregularity of the bowels in 33 per cent.

Anemia is most likely to occur in infections with *Dibothriocephalus latus*, less likely with *T. saginata*, and is said by some authors not to occur with *T. solium*.

Unequal pupils are very commonly recorded; disorders in vision, as narrowing of visual field, amaurosis, monocular polyopia, are on record. Ringing or humming in the ears, disturbances in hearing, and deafness are mentioned. Headache is more or less common (14 per cent., Hirsch); Seeger reports periodical and habitual headache, usually unilateral (19 per cent.) and vague pains in different parts of body (11 per cent.). Itching and dryness of the nose and epistaxis are more or less common. According to Davaine, anal pruritus, like nasal pruritus, may be attributed to a sympathetic influence, but is usually due to irritation of the lining of the lower part of the intestine produced by contact and movement of detached segments; nasal pruritus (12 per cent., Hirsch) is less frequent than anal pruritus (19 per cent., Hirsch), but it is rare that a patient has neither (Davaine).

¹ The statistics quoted from Cobbold (1883 *a*), Hirsch (1879), and Seeger (1852) are based upon infections with large tapeworms and to a certain extent represent selected cases. Ransom (1904 *d*) has published a very instructive compilation of the symptoms reported for 49 cases of infection with the dwarf tapeworm; the reader is referred to Ransom's paper for details since so many complex factors enter into consideration that to quote these details, not all taken from one observer, in comparison with the statistics quoted for the large tapeworms, would require a lengthy discussion extending beyond the limits prescribed for this article. In general it may be said that the same symptoms recorded for the large tapeworms may occur also in connection with the dwarf tapeworm.

Emaciation is common when the infection is of long standing and may be accompanied by bloating and distension of the abdomen. There may be gradual loss of strength, a general and continued weariness, or weakness, especially in the knees; cramps and pains in the limbs may be severe enough to interfere with the usual occupation (Davaïne). Disturbed sleep is common; complete insomnia or abnormal sleepiness may be present in about 1 per cent. (Hirsch); insomnia may be persistent. Vertigo, which many authors mention, Seeger records in 15 per cent.; Hirsch in 16 per cent. Epileptiform attacks (*epilepsia taeniosa*) are mentioned by a number of authors; the symptom is rare (1 per cent. Hirsch), and may occur in patients as young as three years (Comby): the attacks do not attain the severity of true epilepsy; the aura is of long duration, the convulsions may last ten to fifteen minutes and the stage of coma is equally long; all stages are more prolonged than in ordinary epilepsy (Comby) and there is a tendency to periodicity (Martha, 1892).

Treatment.¹—Emphasis may again be laid upon the point that if *T. solium* is present, especially in patients with a tendency to vomit, no time should be lost in expelling the worm; in case of infection with any of the other species mentioned, prompt treatment is advisable on general principles but a postponement for a few days or even a few weeks or months is of less serious moment. During such period, however, the patient should have a care not to defecate in any place where the eggs in his discharge can gain access to the intermediate host.

Special precautions are to be taken, or the treatment is to be indefinitely postponed, according to circumstances, in cases of pregnancy, or in patients especially debilitated from other cause than teniasis, and in convalescence, tuberculosis, and cancer.

Having decided upon treatment, four points in particular are to be held in mind: (1) make it clear to the patient *from the outset* that the expulsion of the worm is to some extent a matter of chance, and that while it may be hoped that only one treatment will be necessary, no physician can possibly foresee whether or not it may be necessary to repeat medication several or many times, especially for *T. saginata*, before a complete cure is effected; (2) the clearer the bowels are the better the chances for expelling the parasites; (3) the older the drugs the less are the chances for success; (4) the tapeworm is an animal with a highly organized nervous system. Corresponding to these important facts, there are four periods in treatment.

1. **Mental Attitude of Patient.**—Gain the confidence of the patient, put his mind at rest on the fact that the disgrace in tapeworm infection does not consist in becoming infected but in not making an effort, by treatment or by care in defecation, to prevent spreading the parasite to other persons. Forewarn the patient that one or several treatments may be necessary.

2. **Preparatory Treatment.**—Place the patient on a light diet for two or three days, avoiding bread and vegetables and such food as is likely

¹ See also remarks under the various species discussed.

to increase the fecal material; allow chiefly liquid diet, milk, broths, eggs, etc. Many physicians prefer, not without good reason, to withhold food absolutely for twenty-four hours preceding the administration of the anthelmintic. At the same time give a mild laxative, such as a few doses of sulphate of soda, or a teaspoonful of compound licorice powder in water in the mornings, and take every precaution to empty the bowels thoroughly, as by a saline purgative the night before the anthelmintic treatment, and enemata the night before and the morning of treatment. The object of this is twofold: the smaller amount of contents in the small intestines the less the tapeworm is protected from the drug; and if the worm meets with an obstruction as it descends, it may have a chance to recover its hold and thus remain in the intestines. Some authors advise a salad of dried herring, garlic, and onions the night before treatment.

3. Anthelmintic Period.—Early in the morning, following the period of preparation, coffee may be allowed but no solid food. Then take any one of the standard teniafuges, provided it is fresh. For the comfort of the patient it is well for him to remain in bed or on a couch during this period, as various disagreeable symptoms (syncope, vertigo, vomiting) may otherwise arise.

Of the numerous tapeworm remedies, certain are recognized as more or less standard, but it would be difficult to obtain a great majority vote for any one of them to the exclusion of the others. The following are among those which are most popular:

Male Fern.—This is perhaps the most commonly used drug in this country and parts of Europe for the expulsion of *Taenia* and *Dibothriocephalus*. In Europe larger doses are administered than in America. Its oleoresin or ethereal extract is usually given and should be fresh. The dose is 2 to 8 grams ($\frac{1}{2}$ to 2 drams) either in a simple syrup or in gram gelatin capsules, which may be coated with keratin in order to prevent their solution in the stomach and thus have the drug reach the worm in more concentrated form; the capsules are taken at intervals of about fifteen minutes. In an overdose, male fern is a distinct poison and it is reported that 24 grams (6 drams) have caused death. Some authors advise that the dose should never exceed 10 grams ($2\frac{1}{2}$ drams), while others maintain that doses higher than 8 grams (2 drams) are both unnecessary and not devoid of danger. Authors also advise against its administration two days in succession and on an absolutely empty stomach. Some authors advise its administration in pills. The last dose should be followed in thirty to sixty minutes by a full dose of salts (as magnesium sulphate) or calomel and salts, rather than with oil which increases its absorption.

Cusso (Kosso or Koussou).—This drug is used most frequently in certain parts of Africa and is highly recommended by several prominent authors. It must be quite fresh. Heller prefers it, and Tyson (1903) says that in his hands cusso "has been decidedly the most efficient" remedy. It should never be given in case of pregnancy. Dose 20¹

¹ Some authors advise only one-fourth to one-half this amount, but writers who are high in the praise of cusso give large doses.

grams (5 drams) for *T. solium*, 30 grams (7.5 drams) for *T. saginata*. There are several "best" methods of administering it. One is to make an infusion in 240 cc. (8 ounces) of water; a more pleasant method is to give 5 grams (75 grains) in a glass of white wine every half hour until four doses are taken; or it may be mixed with honey, enclosed in capsules, compressed into tablets, or combined with male fern.

Generally this requires no purgative but if no movement of the bowels has taken place after six hours, castor oil, compound jalap powder, or elaterium is given.

Kamala.—Kamala is administered in doses of 4 to 8 grams (1 to 2 drams), in syrup or cinnamon water, sweetened coffee or tea, or the fluidextract (2 to 4 cc. — $\frac{1}{2}$ to 1 dram) is given. It is purgative and may cause nausea, vomiting, and griping.

Bark of Fresh Pomegranate Root.—This is given third place by Tyson. Hemmeter advises 50 grams ($1\frac{2}{3}$ ounces), macerated for twenty-four hours in 500 cc. (16 ounces) of water; then evaporate down to 250 cc. (8 ounces) and add syrup of orange peel, 30 grams (1 ounce); to be taken in two parts. It often causes nausea, giddiness or faintness. The fluid extract, 2 to 8 cc. ($\frac{1}{2}$ to 2 drams) is a more convenient dose. Pelletierine, an alkaloid prepared from pomegranate, is especially popular in France. It is given in doses of 0.3 to 1.3 grams (5 to 20 grains). Tanret's preparation is the most popular but none except fresh importations should be used. The efficacy of the tannate is said to be increased and its toxic action diminished by preceding it with a few grains of tannic acid. Pomegranate preparations should be followed within an hour by a brisk cathartic. Some authors give half an ounce of magnesium sulphate twenty minutes before and the same dose twenty minutes after the pelletierine.

Decorticated Pumpkin Seed.—This is an old and rather popular remedy, which has been known to expel *T. saginata* when the foregoing drugs have repeatedly failed; it is the safest and a good drug for children. It is given in various ways: (a) 30 to 120 grams (1 to 4 ounces) of the seed are crushed and given in a strained emulsion followed by a brisk purgative. (b) The seeds are made into an electuary, "which is almost as pleasant as sugar candy, and often about as effectual" (Tyson, 1903). (c) Seeds are carried in the pocket and eaten at short intervals for two or three days until the worm passes. Some authors advise that pumpkin seed be preceded by castor oil or by effervescent magnesium citrate, this to be repeated two hours after the anthelmintic if the tapeworm has not been expelled.

Santonin is advised by some authors, but the writer, in experiments upon himself (with *T. saginata*) found it useless. *Thymol* has been recommended by various authors, but in laboratory experiments upon dogs, the writer has failed to obtain positive results (infection with *Dipylidium caninum*); this drug has, however, given fairly good results at the Marine Hospital in Wilmington, in infections with *Hymenolepis nana*. Naphthalin has its admirers (dose 0.1 to 0.6 gram—2 to 10 grains—followed in an hour by a cathartic). *Cocoanut* has been gaining in repute; the entire milk and meat of one cocoanut are taken, followed by

a purge. Chloroform, oil of turpentine (with equal or twice the quantity of castor oil), zinc filings in syrup, oil of pine needles, and various other drugs have their advocates.

4. **Expulsion.**—The patient should be instructed to use a vessel containing *warm* water while passing the worm and under no circumstances to pass it into a water closet, a privy, or a cold chamber. If the worm comes in contact with a cold object, while a portion of its body is still in the warm intestines, it may contract so suddenly and violently as to break; the head may thus remain in the bowels. The patient should be further instructed not to pull on the worm, should this be coming slowly, but rather to use injections of warm water. If the physician is present during the passage of the worm, the *parasite* is sometimes given an injection of morphine. Finally the patient should submit the entire stool to the physician for examination. Search is made for the head, to determine whether the treatment has been entirely successful. Should the head not be found, it is still possible that it has been passed, so that it is unnecessary to repeat treatment until (after several months) segments or eggs again appear in the stools.

Treatment of Children.—The treatment of children is attended with greater difficulty than the treatment of adults. Comby advises cusso, 10 grams (2.5 drams), or decoction of fresh pomegranate bark, 15 to 20 grams (4 to 5 drams), or ethereal extract of male fern, 4 to 6 grams (1 to 1.5 drams), or pumpkin seed in emulsion 50 to 60 grams (1.66 to 2 ounces). Comby gives ethereal extract of male fern, 4 grams (1 dram), essence of turpentine, 1 gram (15 minims), syrup of orange flower 30 grams (1 ounce), peppermint water, 70 cc. (2.33 ounces); taken at one dose by child five to ten years old and followed in half an hour by 15 to 20 grams (4 to 5 drams) of castor oil (see, however, p. 261). French prefers, for children, drugs in the following order: pumpkin seed mush, cocoanut, black oxide of copper, pelletierine.

SOMATIC TENIASIS

Somatic teniasis, due to infection with the larval stage of tapeworms, may be of three kinds (in order of their importance); hydatid disease, due to infection with the larval *Echinococcus granulosus*; cysticercosis, due to infection with the larval *Taenia solium*, known as *Cysticercus cellulosae*; and infection with bothriocephalid larvæ, classified as *Sparganum mansoni*, *S. baxteri*, and *S. proliferum*.

Cysticercosis or Infection with Larval *Taenia solium*.—The Larval Parasite.—In the early days of helminthology, what we now know to be the larval stage of *Taenia solium* was supposed to represent a distinct species of animal, to which the name *Cysticercus cellulosae* was given. This larva is an elliptical, translucent, bladder-like structure, 6 to 12 mm. long by 5 to 10 mm. broad, with a white spot at its equator, due to the invaginated head. While it usually agrees with the same organism as found in hogs, it may (particularly when located in the subarachnoid spaces) grow to a larger size and assume an irregularly branched form, described as *C. racemosus*. The parasite inhabits the subcutaneous

connective tissue, muscles, brain, spinal canal, eye, heart, lymphatic glands, tongue, liver, bones, lungs, kidney, mammary gland, or prepuce, producing symptoms which vary with the location and number of parasites present. In some cases, especially in very light infections, no symptoms may be observed and the infection is discovered at autopsy. In other instances, particularly in case of location in the brain or eye, the infection is of more importance and in case of cerebral or cardiac infection it may result fatally. If the parasite is in the eye, it is likely to be discovered by the ophthalmologist. In cerebral infection the symptoms are varied according to the exact location; in case of continued pain in the head, visual disorders, mental disorders, with depression and confusion or dizziness, unilateral paralysis, epileptiform, subacute, cumulative spasms, especially in patients over forty years of age, and showing concurrent adult *Taenia solium* in the intestine, or recent history of such intestinal infection, the possibility of infection with the larval stage should be borne in mind.

It takes about three months for the parasite to develop from the six-hooked embryo (onchosphere) to the bladderworm stage, which may live in man as long as twenty years. A patient may harbor from one to several thousand bladderworms, the heavy infection probably representing cases in which an entire segment of the tapeworm has gained access to the stomach through the pylorus. Cysticercosis is decreasing with the decrease of the adult worm; the latter is decreasing as a result of meat inspection and better curing and cooking of pork.

There is no medical treatment; Feletti (1894 *a*) claims good results with male fern, 1 to 3 grams (15 to 45 grains) for several days, but his conclusions require confirmation. Surgical interference may be resorted to if the parasite can be located. Cases of extractions of bladderworms from the eye are recorded.

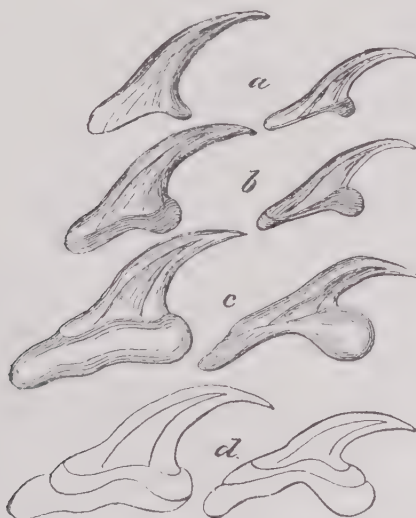
Cysticercus boris, the larval stage of *T. saginata*, is alleged to have occurred in man, but as *C. cellulosae* may lose its hooks and thus resemble the larval stage of *T. saginata*, doubts arise regarding the correctness of the determinations. *Cysticercus acanthotrias* Weinland, 1858, characterized by the presence of three rows of hooks on the head, and taken as the type of a special genus *Acanthotrias*, is now interpreted as simply an anomaly of *C. cellulosae*. *T. hydatigena* (Batsch, 1786), is a tapeworm very closely allied to *T. solium*, with which it was for years confused. The mature worm lives in dogs; the larval stage, known as *C. tenuicollis*, is found in cattle, sheep, hogs, etc., and is reported for certain monkeys; the cysticercus has also been reported for man, but the correctness of the zoölogical determination has been called into question.

Echinococcosis: Echinococcus Disease; Hydatid Disease.—**Geographical Distribution.**—This infection is practically cosmopolitan, but is found especially in Iceland, certain parts of Germany, and in Australia. Many of the cases reported for the United States have occurred in immigrants who were doubtless infected before they came here, but we also have the parasite as part of our American fauna.

Zoölogical Distribution.—The adult tapeworm occurs in the upper half of the small intestine, but never close to the stomach, of dogs,

wolves, jackals, *Canis dingo*, and it can develop in cats. The larval stage occurs in quite a number of domesticated animals, as sheep, cattle, hogs, and also in certain wild animals, being reported in all from twenty-seven species of mammals. From the public health point of view it is especially the dog, sheep, cattle, and swine which come into consideration. Man is probably an accidental though not a rare host.

FIG. 27



Hooks of hydatid tapeworm: *a*, from a hydatid; *b*, three weeks after feeding to a dog; *c*, from an adult; *d*, combined figures of *a* to *c*, showing the gradual changes in form. $\times 600$. (Leuckart.)

The Parasite.—It is at present an open question whether one, two, or three distinct species or varieties of echinococcus should be recognized. Most zoölogists admit only one species, commonly known as *T. echinococcus* (Zeder, 1803) Siebold, 1853, but the writer agrees with Weinland that it is well to place this in a distinct genus; if this is done the correct name of the species is *Echinococcus granulosus*¹ (Batsch, 1786) Zeder, 1803. This is one of the smallest tapeworms known. It is composed of a head with 28 to 50 hooks, a short neck, and 3 or 4 segments; the first segment is immature, the second is mature, the last segment is gravid and it composes about $\frac{1}{2}$ (2 mm.) of the total length (2.5 to 5 mm.) of the worm. The larval stage of this worm is the largest larval cestode known, and is the *Echinococcus*² or *Echinococcus* hydatid of medical and zoölogical authors. This may assume a number of different variations in growth. One of the peculiar extreme forms, the multilocular echinococcus, is recognized by some authors as a distinct parasite but

¹ GENERIC SYNONYMS.—*Echinococcus* Rudolphi, 1802; *Acephalocystis* Laennee, 1804.

SPECIFIC SYNONYMS.—Adult: *Taenia nana* van Beneden, 1861 (not Siebold, 1853); *T. echinococcus* (Zeder, 1803) Siebold, 1853; *Echinococcifer echinococcus* (Zeder) Weinland, 1861.

² *E. polymorphus* Diesing, 1850; *E. unilocularis* Huber, 1896; *E. cysticus* Huber, 1891.

many writers question its right to distinct rank. It would seem to the writer that the present evidence, based largely upon geographical distribution and the larva, more than the adult stage, entitles it to rank as a sub-species, possibly as a species. If recognized as of sub-specific rank the correct name is *Echinococcus granulosis multilocularis*;¹ if recognized as a distinct species the correct name is *Echinococcus multi-*

FIG. 28

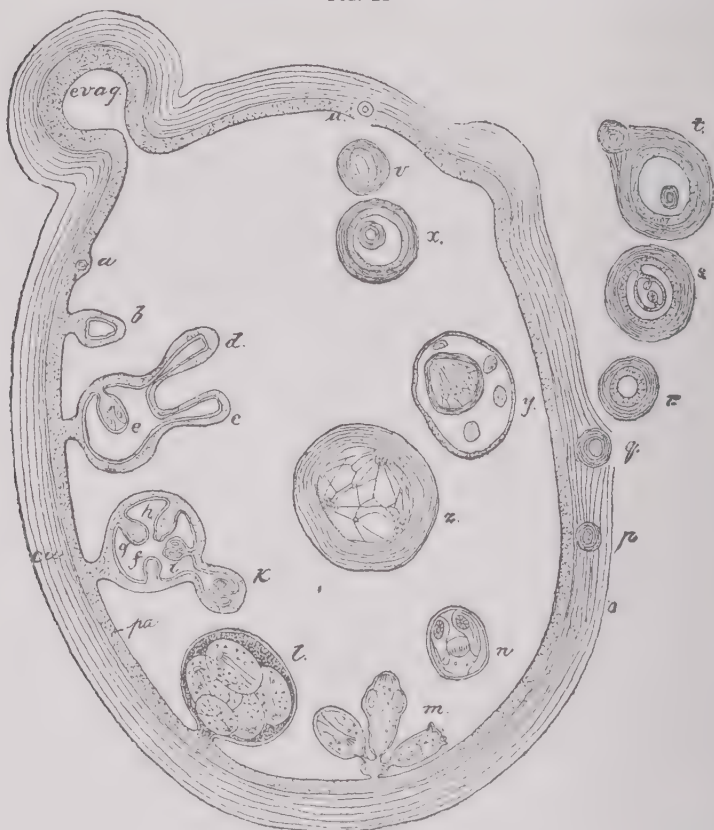


Diagram of an *Echinococcus* hydatid: *cu*, thick external cuticle; *pa*, parenchym (germinal) layer; *c*, *d*, *e*, development of the heads according to Leuckart; *f*, *g*, *h*, *i*, *k*, development of the heads according to Moniez; *l*, fully developed brood capsule with heads; *m*, the brood capsule has ruptured, and the heads hang in the lumen of the hydatid; *n*, liberated head floating in the hydatid; *o*, *p*, *q*, *r*, *s*, mode of formation of secondary exogenous daughter-cyst; *t*, daughter-cyst, with one endogenous and one exogenous granddaughter-cyst; *u*, *v*, *x*, formation of exogenous cyst, after Kuhn and Davaine; *y*, *z*, formation of endogenous daughter-cysts, after Naunyn and Leuckart; *y*, at the expense of a head; *z*, from a brood capsule; *eva*., constricted portion of the mother-cyst. (R. Blanchard, slightly modified.)

locularis. The finer points of distinction between the adult of this form and the typical form call for further investigation; the larval form or multilocular echinococcus is the "Gallertkrebs," "alveolar colloid" or "colloid cancer," usually found in the liver and reported in man,

¹ SYNONYMS.—*Echinococcus multilocularis*; *E. alveolaris*; *E. multilocularis exulcerans* Huber, 1896; *E. osteoklastes* Huber, 1896.

especially for Russia, Bavaria, Switzerland, Württemberg, Austria, the Alps, and Baden.

Von Ledenfeld (1886) states that an echinococcus tapeworm occurs in the dingo in Australia and may attain 10 to 30 mm. in length. The writer has not examined these worms, but unless confusion has here occurred with some other species, he would incline to the view that this parasite represented a distinct species.

Life-cycle of the Parasite and Source of Infection.—The gravid, terminal segment of the tapeworm is discharged in the feces of the dog, and the egg, which is said not to be very resistant, gains access to the intermediate host (sheep, cattle, hogs, man, etc.) through contaminated food or drinking water, or in the case of man, possibly also from hands soiled while petting dogs. Upon arriving in the stomach, the oncosphere (six-hooked embryo) escapes from the shell and, by means of its hooks, bores its way to various parts of the body, especially to the liver. Here it comes to rest and increasing gradually in size it presents a thick outer cuticle and an inner parenchymatic layer surrounding a cavity containing fluid. An outer connective-tissue cyst is furnished by the host. This simple form is known as an *Acephalocystis* Laennec, 1804. Brood capsules arise from the parenchymatic layer and hang into the cavity; heads form in these brood capsules. If this stage is fed to dogs each head develops into a tapeworm. The growth of the hydatid need not stop at the stage last mentioned but daughter-cysts and even granddaughter-cysts may form and fall into the cavity of the mother-cyst; this variation represents the endogenous echinococcus,¹ and is the more common variation as it occurs in man; it may attain 22 to 33 pounds in weight; the daughter-cysts may be numerous, "twenty-five to fifty" or up to "thousands." In still other cases the daughter-cysts pass outside of the mother-cyst into the surrounding tissue, thus giving rise to the exogenous echinococcus,² rather infrequent in man but more common in ruminants, pigs, and the horse. It occurs in the omentum, peritoneum, kidneys, mammary gland, and brain, exceptionally in the liver, but it never attains the enormous size sometimes seen in the endogenous variation.

Frequency.—We are hardly able to give even approximate statistics covering the frequency of echinococcus infection in the United States. The writer recalls one abattoir (in Kansas City) where this infection in hogs was estimated several years ago at 1 per cent. This would indicate that in certain rural localities, indigenous cases have probably occurred in man which have escaped attention. Several years ago a former assistant (H. O. Somer) of the writer collated 100 cases in man for the United States and 12 cases for Canada, but as 33 of the United States cases were reported for New York alone, these statistics must surely cover only a percentage of the actual cases; they further show quite a percentage as having been found in foreigners, and as probably many, if not most of these latter brought their infection with them to

¹ *E. altricipariens* Küchenmeister, 1855; *E. hominis* (Zeder, 1800) Rudolphi, 1810. *Echinococcus endogena* (Kuhn, 1830); *E. hydatidosus* Leuckart, 1863.

² *Echinococcus granulosus* (Batsch, 1786) Rudolphi, 1805; *E. veterinorum* Rudolphi, 1810; *E. exogena* (Kuhn, 1830); *E. scolecipariens* Küchenmeister, 1855.

this country, the figures can hardly be taken as representing American conditions. We may expect more cases in rural and village districts in which the "country slaughter-house" flourishes. In Manitoba, the infection has been common among the Icelanders. Of the English-speaking countries, Australia has presented the highest figures; the province of Victoria, for instance, is said to have 3 per 1000 mortality from hydatids and 1 case of echinococcus for every 175 hospital patients, while 1.61 to 2.73 per cent. mortality is said to occur in South Australia. The estimate of 400 deaths per year for England is very difficult to accept, especially in view of the comparatively few articles on this disease in the current English medical journals, but Huber quotes Murchison as reporting about 1.5 per cent. infection in his postmortem examinations. In certain parts of Continental Europe, echinococcus disease is not uncommon; thus Madelung reports for Rostock 1 case per 1056 inhabitants; from 1861 to 1883, Rostock also showed 25 postmortem cases in 1026 autopsies, or 2.43 per cent.; and the slaughter-house statistics for entire Germany give an average of 10.39 per cent. for cattle, 9.83 per cent. for sheep, and 6.47 per cent. for hogs.

Iceland is recognized as the classical echinococcus land, but some of the published estimates must be taken with reserve. The more conservative statistics give the infection as from 1 in 43 to 1 in 63 of the inhabitants, and Krabbe reports the adult worm in 25 per cent. of the dogs. Hydatids seem to be more common in females than in males, but some statistics give them as more common in males, and according to Meisser, they occur more commonly in patients from twenty-one to thirty years of age (about 30.8 per cent. of the cases collected).

The parasite is most commonly located in the liver. Thus of 1806 organ-infections, the following organs were the most frequently affected: liver (1011), lung (147), and kidney (126); the parasite can, however, develop in any portion of the body.

Duration.—The growth of the echinococcus is very slow; according to Leuckart's experiments on swine, it takes five months for the cyst to reach a diameter of 15 to 20 mm. If scolices are fed to dogs, the development of the adult worm is also slow; about ten to twelve weeks may be required for the worm to reach the gravid stage. How long a hydatid cyst might live in man is an open question; it has been stated that 50 per cent. of the infections are fatal within five years, but as many cases are doubtless not diagnosed, statistics on this point are always open to some question. Authority exists for cases in man of two to eight years' duration and even longer.

Symptoms.—The symptoms of echinococcus disease are practically those of a slowly growing tumor, which may attain 22 to 44 pounds in weight and which causes different symptoms according to its location. In some cases the worm may die, the parasite then collapses, and the cyst becomes gelatinous and thick; the heads, or at least the hooks, may be found in the altered, thick, opaque contents. In some cases the cyst may suppurate. The hydatids are occasionally discharged through various channels (bile-ducts, lungs, in urine, etc.). Urticaria may develop upon the rupture or puncture of the cyst admitting the echino-

coccus fluid into the body cavity, but it is said to occur also in case of apparently uninjured cysts.

Diagnosis.—In many, but not all cases, the so-called hydatid thrill or fremitus is felt on percussion, resembling the quivering of jelly. Deeply seated echinococci give an elastic feeling, superficial parasites a fluctuation. Positive diagnosis may be made microscopically by finding the hooks or heads in case of discharge, or in the aspirated fluid; and presumptive diagnosis may be made by finding sugar in the aspirated fluid. The multilocular echinococcus is usually in the liver and accompanied by a chronic icterus.

Serodiagnosis appears to be a valuable method in diagnosis, and there is extensive recent literature on the methods. Weinberg and others show that the fixation of the complement is a much more delicate test of the presence of antibodies in the serum of patients than is the precipitin test. This reaction sometimes fails, especially in cases in which the cyst has suppurated. Bettencourt, by applying a hemolytic system of human red blood corpuscles and a rabbit-homo-serum, similar to that suggested by Noguchi for syphilis, has obtained positive reactions, confirmed by operation in cases where the precipitin and the Bordet-Gengou reactions have failed.

Treatment.—Numerous methods of medicinal treatment have been proposed for hydatid disease, all having one attribute in common: namely, apparent uselessness. Echinococcus infection is a surgical disease and only surgical interference is capable of curing it. Several authors refer to "boldly incising the cyst," but attention may be directed to the fact that by opening the external cyst (namely, the surrounding cyst which is furnished by the host) very cautiously, the inner cyst (namely, the parasite itself) can be taken out entire; to do this the external cyst should be raised at a convenient point, leaving a small space between it and the inner cyst. Strictly aseptic tapping has been followed by recovery. In the event of suppuration the condition is treated as one of abscess.

Prevention.—Since this disease is transmitted from dogs to man, and since dogs obtain their infection more particularly from eating the infected organs of slaughtered sheep, cattle, and hogs, it is clear that any plan of prevention should follow two lines: *First* and most important, dogs should be kept away from slaughter-houses in order to prevent them from eating the organs rejected on account of hydatid infection; the rule that no dog which enters a slaughter-house or its refuse yard should ever be allowed to leave would, if carried out, save many lives and much valuable live stock, but it is difficult of practical application. *Secondly*, whatever our affection may be for "Old Dog Tray," we should recall that he is a dog and not a human being; in his place he is useful, but out of his place he may be a very dangerous friend.

So far as can be judged from the federal meat inspection, hydatid disease is much more common than is generally supposed. The writer recalls one abattoir where the infection among the hogs was estimated at 1 per cent.; with this percentage it seems positive that in some sections of the country the parasite has developed to such an extent that local

boards of health should institute measures for its control by placing the local slaughter-houses under sanitary supervision.

Sparganum Mansonii (Cobbold, 1882) is a larval bothriocephalide tapeworm reported 10 times¹ in the Japanese. It measures 8 to 36 cm. in length by 0.1 to 12 mm. in breadth, and 0.5 to 1.75 mm. in thickness; it is flat and unsegmented and as yet no stage with genital organs has been found. It occurs in the subperitoneal connective tissue and body cavity of man in Amoy and Japan. Sonsino reports it for the jackal in Egypt. Daniels found this or a similar parasite in British Guiana.

The parasite was lodged in the region of the eye in 3 cases; it escaped from the urethra in 4 cases; was in the connective tissue of abdominal region in 1 case and in the pleural cavity in 1 case. A single parasite was reported in 9 cases, 12 parasites in 1 case.

Surgical treatment should be used in superficial swellings, while in urethral cases the worm should be extracted while the patient is in a warm bath, the parasite being slowly drawn out or wound around a stick under water. It might perhaps be well to give the parasite a hypodermic injection of morphine shortly before pulling it out.

Sparganum baxteri (Sambon, 1907 *b*) is reported as indistinguishable morphologically from *S. mansonii*. It was found in an abscess on the thigh of a Massi in German East Africa. Similar parasites were found in the body cavity of an African snake (*Bitis nasicornis*).

Sparganum proliferum² (Ijima, 1905) is a peculiar larval cestode first reported for Japan. It occurred in the subcutaneous tissue, especially of the leg, and produced acne-like swelling and a condition somewhat similar to elephantiasis. The worms measure 1 to 12 mm. long by 2.5 mm. in breadth, and possess the peculiarity of reproducing by budding. Adults and life history are unknown.

A second case, of twenty-six years' standing and finally fatal, occurred in Florida. Upon autopsy the cadaver would have appeared emaciated had it not been for the enormous number of worms that filled the fat spaces so that the body had the appearance of being well nourished. The infection was almost generalized, extending even to the brain. The parasites reproduced in the larval stage by budding. A third case is said to have been found in Japan. So far as can be foreseen at present, the infection *appears* to be theoretically fatal.

ROUNDWORM INFECTION—NEMATHELMINTHES

The roundworms are divided into three orders (see key, p. 222): namely, the *Nematoda*, the *Gordiacca*, and the *Acanthocephali*. Of these, the nematodes are by far the most important, while the horse-hair worms and the thorn-headed worms are of secondary importance in human medicine. For practical reasons they will be arranged in this article according to the part of the body they inhabit instead of according

¹ For compilation of cases to date, see Stiles and Tayler, 1902 *b*, pp. 47 to 56, Figs. 30 to 36.

² SYNONYMS.—*Plerocercoides prolifer* Ijima, 1905; *Plerocercus prolifer* Ijima, 1905. For full discussion in English, see Stiles, 1908 *c*, *Bulletin* 40, Hygienic Laboratory.

to their zoölogical arrangement. Systematically the roundworms parasitic in man are classified in the following families and genera:

- Family Anguillulidae: genera *Anguillula*, p. 315; *Anguillulina*, p. 294; *Leptodera*, 316; *Rhabdilis*, 295, 303.
- Fam. Angiostomidae: genus *Strongyloides*, p. 285.
- Fam. Gnathostomidae: genus *Gnathostoma*, p. 302.
- Fam. Filariidae: genera *Filaria*, p. 305; (*Microfilaria*, p. 305); *Setaria*, p. 302; *Dirofilaria*, 314; *Onchocerca*, p. 314; *Dracunculus*, p. 303; *Agamofilaria*, p. 314.
- Fam. Trichinellidae: genera *Trichinella*, p. 297; *Trichuris*, p. 295.
- Fam. Strongylidae s. l.: genera *Strongylus*, p. 294; *Metastrongylus*, p. 302; *Haemonchus*, p. 294; *Trichostrongylus*, p. 294; *Oesophagostomum*, p. 294; *Ancylostoma*, p. 274; *Necator*, p. 272; *Triodontophorus*, *Physaloptera*, p. 293.
- Fam. Dioctophymidae: genus *Dioctophyme*, p. 316.
- Fam. Ascaridae: genera *Ascaris*, p. 287; *Toxocara*, p. 288; *Belascaris*, p. 288; *Toxascaris*, p. 288; *Lagochilascaris*, p. 288; *Oxyuris*, p. 291.
- Fam. Mermithidae: genera *Mermis*, p. 296; *Agamomermis*, p. 296.
- Fam. Gordiidae: genera *Gordius*, p. 296; *Paragordius*, p. 296; *Parachordodes*, p. 296.
- Fam. Gigantorhynchidae: genus *Gigantorhynchus*, p. 297.
- Fam. Echinorhynchidae: genus *Echinorhynchus*, p. 297.

INTESTINAL ROUNDWORMS

Uncinariasis¹ or Hookworm Disease.—Geographical Distribution.²

Uncinariasis encircles the globe in the tropical and subtropical belt, diminishing in frequency in the temperature climates, but occurring locally in mines as far north as Great Britain, Holland, and Germany in Europe; in North America the endemic infection stops about at the Potomac River.

Zoölogical Distribution. Generically identical, but specifically distinct infections occur in dogs, cats, foxes, and various other animals. The infection of cats, which was supposed to be specifically identical with the Old World hookworm of man, has proved to be distinct, and the infection of the chimpanzee, reported by Linstow and supposed to be identical with the New World hookworm of man, is also distinct.

The Parasites.—Hookworm disease in man is due to two distinct species of parasites belonging to the subfamily Uncinariinae,³ namely, the Old World hookworm and the New World hookworm.

¹ SYNONYMS.—Anchylostomiasis; ankylostomiasis; brickmakers' anemia; dirt eating (in part); dochmiosis; Egyptian chlorosis; geophagia (in part); malarial anemia (in part); malnutrition (in part); miners' anemia; miners' cachexia; negro consumption; St. Gothard tunnel disease; tropical chlorosis; tunnel anemia; tunnel disease.

For literature on this disease, apply to the Rockefeller Sanitary Commission for the Eradication of Hookworm Disease (Washington, D. C.), to the U. S. Public Health Service (Washington, D. C.), or to the State Board of Health of any Southern State from Virginia to Texas. These publications, profusely illustrated, are distributed gratis and should be in the library of every physician.

² See *Publication No. 6*, Rockefeller Sanitary Commission, 1911.

³ As this group of worms is more carefully studied, it becomes apparent that the old genus *Uncinaria* (type *vulpis* = *criniformis*) must be divided into at least four smaller groups: *Uncinaria* (type *vulpis*), *Ancylostoma* (type *duodenale*), *Necator* (type *americanus*), *Bunostomum* (type *trigonocephalum*), and probably into several additional units. Opinion will probably differ for some time to come as to whether these units represent genera or subgenera, but evidence is accumulating to the effect that they should be given generic rank. Changes in the generic nomenclature in consequence of such division are of course unavoidable, in the same way that a new terminology had to be used when (1860) trichinosis was differentiated from typhoid fever. No change, however, in the specific nomenclature of the two forms (*americanus* and *duodenale*) found in man can be foreseen.

The New World hookworm, *Necator americanus*¹ (Stiles, 1902), is the common hookworm of the American continent and adjacent islands, but it has been introduced into Italy, and doubtless also into Spain. It has been reported recently also for Africa, China, Guam, and elsewhere and is now known to have a very wide distribution. The same parasite

Fig. 31

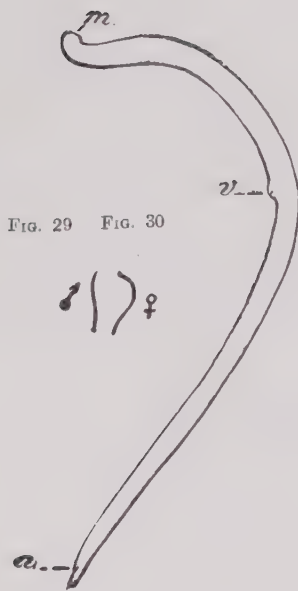


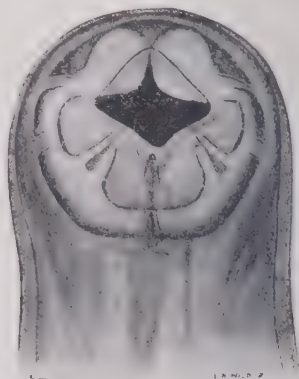
Fig. 29 Fig. 30

FIG. 29.—New World male hookworm. Natural size. (Stiles.)

FIG. 30.—New World female hookworm. Natural size. (Stiles.)

FIG. 31.—The same, enlarged to show the position of the anus (a) and the vulva (v). (Stiles.)

Fig. 32



Head, greatly magnified. We are looking directly into the mouth and see (above) the two jaws, and in the middle of the picture a hollow tooth, somewhat similar to the poison fang of a snake. (Stiles.)

Fig. 33



A side view of the head, greatly magnified and showing the mouth cavity (the very black portion), into which extend the prominent fang-like tooth and the sharp lancets. (Stiles.)

is found in the gorilla. This cylindrical worm is 7 to 11 mm. long and possesses a dorsal and a ventral pair of lips at the mouth, a prominent dorsomedian buccal tooth, and four buccal lancets; in the male, the dorsal

¹ SYNONYMS.—*Uncinaria americana* Stiles, 1902; *Ankylostomum americanum* (Stiles) Linstow, 1903 (exclusive of form in the chimpanzee); *Uncinaria* (*Necator*) *americana* (Stiles); *Necator americanus* (Stiles); *Uncinaria hominis* Ashford, King, and Gutierrez, 1904, in part; *Necator africanus* Harris (not Looss).

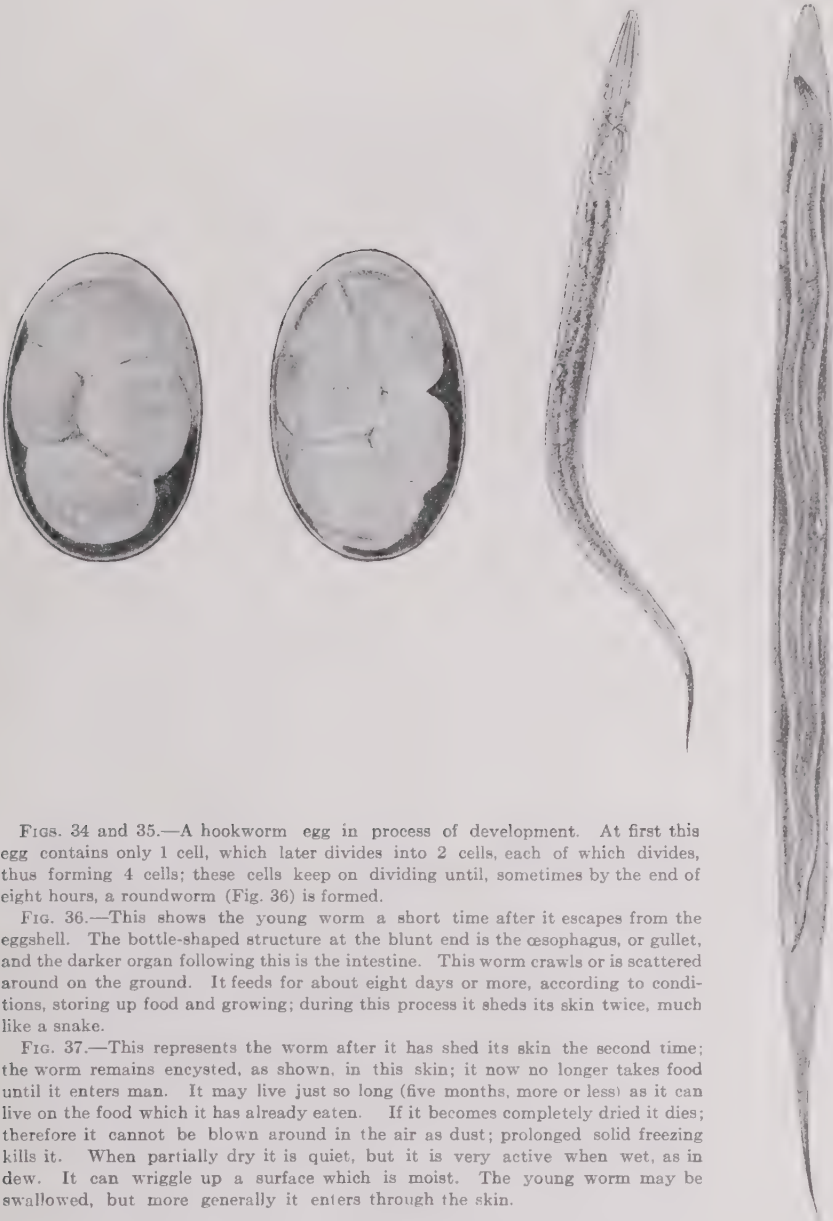
ray of the bursa divides at the base and each branch possesses two tips. In the female the vulva is in the anterior half of the body. The eggs

FIG. 34

FIG. 35

FIG. 36

FIG. 37



FIGS. 34 and 35.—A hookworm egg in process of development. At first this egg contains only 1 cell, which later divides into 2 cells, each of which divides, thus forming 4 cells; these cells keep on dividing until, sometimes by the end of eight hours, a roundworm (Fig. 36) is formed.

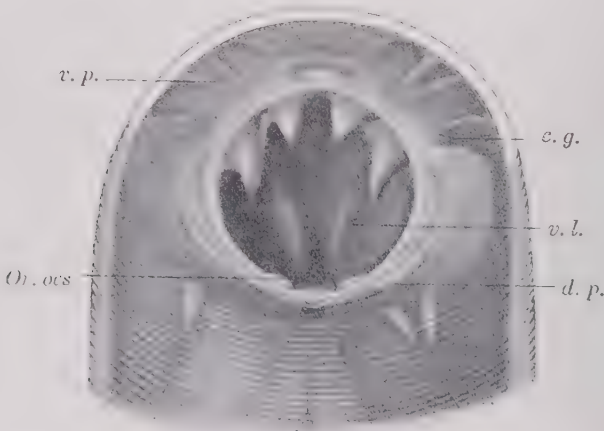
FIG. 36.—This shows the young worm a short time after it escapes from the eggshell. The bottle-shaped structure at the blunt end is the œsophagus, or gullet, and the darker organ following this is the intestine. This worm crawls or is scattered around on the ground. It feeds for about eight days or more, according to conditions, storing up food and growing; during this process it sheds its skin twice, much like a snake.

FIG. 37.—This represents the worm after it has shed its skin the second time; the worm remains encysted, as shown, in this skin; it now no longer takes food until it enters man. It may live just so long (five months, more or less) as it can live on the food which it has already eaten. If it becomes completely dried it dies; therefore it cannot be blown around in the air as dust; prolonged solid freezing kills it. When partially dry it is quiet, but it is very active when wet, as in dew. It can wriggle up a surface which is moist. The young worm may be swallowed, but more generally it enters through the skin.

are thin-shelled, 64 to 72 μ long by 36 to 40 μ broad; they are oval with somewhat bluntly rounded poles.

The Old World hookworm, *Ancylostoma duodenale*¹ Dubini, 1843, is the common hookworm of Egypt and has a wide distribution in Europe, Asia, Africa, and Australia; it has also been introduced to some extent into the Americas. This parasite measures 8 to 18 mm. in length and

FIG. 38



Dorsal view of the Old World hookworm: *c. g.*, opening of cephalic gland; *v. l.*, ventral lancet; *d. p.*, *v. p.*, dorsal and ventral papillæ; note also the four teeth. Greatly enlarged. (Looss.)

possesses in its mouth 2 pairs of strong, curved, ventral teeth and 1 pair of knob-like dorsal teeth; the dorsomedian tooth of the buccal capsule is nil or practically so; a pair of ventral lancets is present in the buccal cavity. In the male, the dorsal ray of the bursa is divided two-thirds

FIG. 39



Six stages in the embryonic development of Old World hookworm; *a-c.* are the stages found in fresh feces. $\times 336$. (Looss.)

its length from the base and each branch is subdivided into three tips. In the female, the vulva is in the caudal half of the body. The eggs measure 52 to 61 μ long by 32 to 38 μ broad; they are oval with very bluntly rounded poles.

¹ SYNONYMS.—*Ancylostoma duodenale* Dubini, 1843; *Ancylostoma duodenale* (Dubini) Creplin, 1845; *Dochmius duodenalis* (Dubini) Leuckart, 1876; *Anchilostoma duodenale* (Dubini) Bozzolo, 1879; *Uncinaria duodenalis* (Dubini) Railliet, 1885; *Ankylostoma duodenale* (Dubini); *Ankylostomum duodenale* (Dubini); *Uncinaria hominis* Ashford, King, and Gutierrez, 1904, in part.

Both parasites inhabit the small intestine, especially the jejunum and ileum but also the duodenum and occasionally the stomach.

Source of Infection.—The eggs are oviposited in the intestine of the patient; they do not develop until after they escape with the feces; then they develop within twenty-four hours or more, according to conditions of heat, moisture and amount of oxygen, a rhabditiform embryo which undergoes ecdysis (shedding of skin) after about forty-eight to seventy-two hours; a second ecdysis which occurs within about five to nine days changes the worm to the infecting stage—the so-called “encysted larva;” from this point the worm takes no more food until it reaches man. Infection takes place in two different ways: (1) It has been experimentally demonstrated, first by Looss, that the hookworm larvæ may pass through the skin, reach the circulatory system, pass with the blood through the heart to the lungs, from the lungs to the air passages, up to the larynx, down the œsophagus to the stomach and then to the small intestine. Looss’ theory of skin infection first met with opposition, but it now stands on the firm foundation of experimental proof and has been generally accepted. Strange and incredible as the view is, it is now not only established as a possible method of infection, but it is the most common method by which hookworms gain access to the system. (2) A second method of infection is through the mouth, either with contaminated food or water or from earth containing the hookworm larvæ and clinging to the hand. Since Looss’ skin infection theory has been proved, the idea of infection through the mouth has lost many supporters, and numerous arguments are submitted to prove that it is of exceptional occurrence. That the time has now come when the skin infection is generally accepted as the more important method, may be admitted, but it does not seem to the writer that we are justified in looking upon infection by the mouth as a curiosity or as a method which can be practically ignored. The skin infection is a brilliant proof of the correctness of an old popular view which obtained regarding infection with certain parasites, a view which was practically abandoned as being too complicated and improbable, when the mouth offered such a simple, probable, and, in some cases, demonstrated entrance for intestinal worms. And it would be wise for us now not to be carried away with these new brilliant discoveries and this demonstration of the correctness of an old-fashioned idea to such an extent that we fall into error of forgetting that worms can and do enter the system by the mouth and that, given the proper conditions, there is no reason at present evident why the hookworm should not be taken into the body in this way, especially in view of the fact that experimental infections per mouth have given positive results.

The view advanced that the free embryos may develop into free adults, the progeny of which become parasitic, is not in harmony with what is otherwise known of this group of worms and may safely be eliminated from consideration.

Frequency.—Uncinariasis is a malady the spread of which is inconsistent with a proper sewage system, cold weather or dry conditions. Accordingly, in general terms, it is more common in moist localities

than in dry, more common in warm countries than in cold, and more common in rural districts than in cities. Although it is one of the worst scourges of the tropics, even there its frequency may be decreased by a proper disposal of feces, for fortunately the specific infections in man are not known for the domesticated animals.

It is more common among people who come into direct contact with damp earth, as farmers, miners, tunnel-diggers, and people who go bare-footed, than it is among persons of other occupations and those who wear shoes.

Many authors report that it is more common among men than among women and children, others that it is more common and more severe in children and in women than in adult males. It is not difficult to harmonize these divergent statements. Physicians reporting for mining districts would, in general, find more cases among the miners (namely, among men), for the infection here occurs chiefly "underground," while the homes in many mining districts are provided with sewage or with proper privies and the miners' families are thus more or less protected from infection. Further, many authors have reported upon cases which came to them for diagnosis and treatment, while other writers have gone to the families in order to find the cases; hence the conditions covered by his reports represent more exactly the natural conditions in the rural districts visited. Again, in rural districts containing more children than adult males, as found in the localities in question, under conditions favorable to infection there would naturally be more cases among the children; furthermore, the children and women were in some instances following a life more conducive to infection (namely, staying near the house, in the area of concentrated infection, more than were the men), and infection would therefore be expected to be more common among the former. In general, frequency varies with the degree of exposure to infection, but certain laboratory experiments and clinical observations seem to indicate that it is not impossible that a difference in intensity and frequency of infection may perhaps be found in different classes even when exposed to apparently the same chances for infection.

Ashford, King, and Gutierrez (1904), in their splendid "Report on Anemia in Porto Rico," found more cases (1027 of 5490) between the ages of five and nine years than at any other five-year period; of the same 5490 patients, 3259, or 59.34 per cent., were males, and 2131, or 40.66 per cent., were females.

In the districts visited by the writer, uncinariasis is preëminently a disease of the piney wood and sand localities, occurring less in clay regions. However, this distribution was not confirmed by Ashford, King, and Gutierrez in Porto Rico. Some of the physicians in the South have confirmed the author's findings in this respect, while others have obtained different results. The explanation of the different findings is not entirely clear at present. There is evidently some factor in the case which has thus far escaped attention, and which will doubtless harmonize the divergent reports. Possibly, Nicholson and Rankin (1904) have given the correct clue when they state that it is not so much a question of the *sandy* nature of the soil as it is a question of *fine* soil

which by its ability to hold moisture offers the most favorable conditions for development. Further, the trees would naturally protect the young worms, to some extent, against the drying effects of the sun. A certain seasonal periodicity is shown insofar that infection decreases in cold and very dry seasons, but increases in warm and moist seasons. Uncinariasis is more common and more severe among the poor than among the well-to-do, and more common among people who live under conditions of filth than among those who live under better hygienic conditions; it should, however, be recalled that neither individual wealth nor individual refinement is a guarantee against infection, but rather that this is to be sought in *community* sanitation.

As for statistics, some physicians in Southern Florida estimate that 90 per cent. of the rural population in that district harbor the parasite to a greater or less degree, and Ashford, King, and Gutierrez estimate that about 90 per cent. of rural population of Porto Rico are infected. Of 158,555 rural school children, examined microscopically in 230 counties in eleven Southern States, 78,572 (50.9 per cent.) showed the infection. In some German mines, 30 to 80 per cent. of the miners have been found infected. So far as known the infection is relatively rare in most American mines.

Pathology.—Aside from the anemic conditions, attention may be directed to the intestinal tract. The stomach is frequently dilated and exhibits a chronic catarrh. One observer speaks of seeing attacks of acute dilatation, especially in children. The small intestines, especially the jejunum and ileum, show a diffuse catarrh of variable severity, and the bites made by the worms; hemorrhages may be present or absent; there may be large spots of hemorrhagic infiltration with a worm hanging from its centre; there is a chronic interstitial inflammation; Ashford, King, and Gutierrez report the intestinal wall as very much thinned but several authors report it as very much thickened; constrictions have been reported in South American literature.

The parasites injure in different ways, but evidence seems to be accumulating in support of the view that their toxic effect is more serious than generally admitted. Loeb and Allen J. Smith have shown that hookworms produce a substance which inhibits the coagulation of the blood. It is not excluded that the condition of the intestines and their contents, due directly or indirectly to the parasites, has been underestimated in respect to its rôle in this disease.

Symptoms.—Cases may be divided into *light*, *medium*, and *severe* infections. Under the *light* infections may be included those patients who show eggs in the feces upon microscopic examination, but who do not exhibit any or sufficiently marked symptoms to attract special attention. These cases, known as "*carriers*," are numerous and are important in that they are capable of keeping a region infected and thus giving rise to severe cases; hence from a prophylactic standpoint, they should always be treated when found. Furthermore, despite the assumed lack of symptoms, indications are not lacking that even "*carriers*" may be influenced to a slight degree in respect to their weight, their mentality, and possibly other factors. Under *medium* cases may

be included those persons who show a definite anemia, while other symptoms, mentioned below, develop to an extent which attract sufficient attention to bring the patient under medical treatment; a physician in the infected district should immediately suspect uncinariasis, but the Northern physician might not be so promptly led to this diagnosis. Under *severe* cases may be classified the typical or near-dirt-eaters who present a clinical picture which even the laity in the South recognize on sight. A fourth class, *very severe* cases, may be recognized if desired, to include those patients in whom death may occur at any moment.

These four phases grade imperceptibly from the lightest to the most severe. The division suggested is a compromise between the classification proposed by the writer in 1902 and that used by Ashford, King, and Gutierrez (1904), and is here adopted from a practical standpoint in prophylaxis in order to lay stress upon that large number of cases in which eggs may be present but no special symptoms noticed; these cases must be constantly kept in mind in any scheme for eradication of the disease, and are likely to be overlooked or ignored unless special attention is directed to them. Thus, it has recently been shown that there are numerous cases of infection which were not even suspected until the microscopic examination was made.

General Development.—If infection occurs before puberty it is likely to retard development both physical and mental. A boy or girl of twelve to fourteen years may appear to be eight to ten and one of eighteen to twenty-two may appear to be not over twelve to sixteen.

Skin.—The skin may be waxy white to dirty yellow, tallow or tan, the color being a general superficial, but not in all cases exact, indication of the degree of anemia. It becomes dry and parchment-like, perspiration being more or less completely suppressed. Petechiae may be observed in older cases. Pruritus may be noticed more or less frequently. Atrophy of the skin is seen in chronic cases.

Ground-itch.—As Bently (1902*a*) pointed out, it is very common to find a history of ground-itch in hookworm districts. Of 4741 Porto Rican patients questioned by Ashford, King, and Gutierrez on this point, 4654 or over 98 per cent. gave a history of "mazamorro," as the dermatitis is called by the natives. "New Sump bunches" in the Cornwall miners is reported by Boycott and Haldane. In our Southern States ground-itch is exceedingly common in some districts, especially during wet weather. The present evidence clearly shows that this rapidly developing condition (characterized by a few itching papules to a severe dermatitis, found more particularly in bare-footed people, between the toes especially and on the sides and top of the foot, and in some cases on the buttocks or other portions of the body) is the initial symptom of uncinariasis, due to the penetration of the larvæ into the skin, and doubtless accompanied in many cases by some bacterial infection. The writer is not aware that any dermatologist has as yet made any special study of ground-itch, and until this is done it will be wise to leave the question open as to whether *all* cases of this affection are due to uncinariasis, especially since *Strongyloides* larvæ, also, may enter the skin; our observations are to the effect that ground-itch (also known

as foot-itch, toe-itch, wet-weather-itch, dew-itch, etc.) includes at least three different conditions.

Hair.—While the hair on the head may be normally developed, it is likely to be dry and harsh, and there may be a marked scarcity or absence of hair on the pubes, in the armpits, and on other parts of the body, in patients who become infected before puberty.

Edema.—Edema of the face, feet, ankles, leg, scrotum, or entire body may be present. According to the Porto Rican (1904) statistics it was most frequently found in patients showing a hemoglobin of 20 to 49 per cent.

Wounds and Ulcers.—In a number of cases, it is noticed that even slight lesions of the skin heal slowly. In severe cases, ulcers (some of them of one to nine years' standing) are not uncommon; they are usually situated on the tibia or on the foot; in some instances they heal promptly after the worms are expelled from the intestine. The question naturally arises whether some cases of so-called hookworm ulcer are in reality "tropical ulcers," and *vice versa*.

Head.—The face may show an anxious, stupid expression. The conjunctivæ may be chalky-white. The pupils have a decided tendency to dilatation; the patient may show a blank stare; night-blindness is reported in a number of cases. The visible mucous membranes vary from a natural color to a white, corresponding more or less to the degree of anemia. Recurrent attacks of epistaxis have been observed. The tongue may show two purplish smears, one on each side of the median lines; pigmented spots and a partial denudation of the epithelium may be observed.

Neck.—Cervical pulsation, especially in severe cases, is very evident, often being visible from six to twelve feet from the patient.

Thorax.—In emaciated cases the ribs are of course very prominent. The infraspinatus muscles are frequently underdeveloped and the scapulæ may show a pronounced "winged" condition.

Abdomen.—A more or less prominent abdomen is rather common, known among the laity as "pot-belly," "butter-milk belly," or "shad-belly," and ascites may develop.

Digestive System.—Appetite: This may be light to ravenous; in late stages there may be complete anorexia. There is a marked tendency to the development of abnormal appetite for sour articles as pickles, or for salt, coffee, and buttermilk, or a perverted appetite for resin, charcoal, chalk, tobacco ashes, dried mortar, mud, clay, sand, gravel, shells, rotten wood, cloth, garments (the writer met one boy who had eaten three coats, thread by thread, within one year), paper, tobacco pipes, and even mice and young rats. Salivation is frequent. Flatulence and heart-burn are common; nausea is frequently reported and vomiting may occur. Pain and tenderness in the epigastrium are mentioned by nearly all observers; Ashford, King, and Gutierrez (1904) give it as "the most constant, most suggestive, and most clearly marked of all the symptoms of the digestive tract." It may be brought into prominence by pressing on the right hypochondrium, or, upon deep inspiration, directly below the ensiform cartilage. Constipation is common, but

diarrhœa may be present. The statements by authors relative to the feces are very contradictory. Ashford, King, and Gutierrez found blood macroscopically in only 6 cases, and blood and mucus in 5 cases, out of over 22,000 fecal examinations, statistics which are far below the conditions observed in the Southern Atlantic States by the writer. Leichtenstern has suggested that the blood is more likely to appear during the period of copulation of the worms. Evidence shows that in some cases blood may be absent, in other cases present, either macroscopically or microscopically, in the stools.

Circulatory System.—Heart: The apex beat is pronounced in the slight grades of the disease; in moderate grades it is often displaced downward and to the left; in marked grades, a notable phenomenon is the great reduction in the force of the apex beat, which is replaced by a wavy, indefinite pulsation in the epigastrium, or a tumultuous heaving of the whole precordium, and in these cases cyanosis, chiefly in the lips, is likely to be noticed; a presystolic thrill is not infrequent in moderate cases, more common in marked cases; in moderate cases, hypertrophy, especially of the left ventricle, causes an enlargement of the heart area; the murmurs are best heard in the third intercostal space; in moderate cases, hemic murmurs are almost always present (Ashford, King, and Gutierrez). Palpitation occurs early and is very prominent and constant. Dyspnea is very common, especially in the later stages. The pulse varies from 80 to 132, without any necessary relation to the temperature; in the later stages it becomes dicrotic, then weak and compressible, finally thready, irregular, and intermittent.

Blood.—The anemia is the most pronounced symptom and has been taken as basis for a number of the vernacular names of the disease; it is natural that recent authors have conducted special studies on the blood. Ashford, King, and Gutierrez (1904) have made a faithful study of the blood conditions. In one series of 540 persons, compared as to race, they found the average *hemoglobin* at over 45 per cent. in whites, over 44 per cent. in mulattoes, and over 49 per cent. in negroes. In a series of 577 persons compared, in reference to sex, the males showed an average of 41 per cent. hemoglobin; females, 48 per cent. Of one series of 579 cases, the hemoglobin upon later examination during treatment showed an increase in 371 cases from 1 to 71 per cent., average 21.34 per cent.; 7 cases neither gained nor lost; a weekly increase of 20 to 30 per cent. was not rare. During the disease, the hemoglobin falls before the red cell count and may reach as low as 30 per cent. before much change in the reds is noticed; under treatment the reds usually increase more rapidly than the hemoglobin.

The red cells vary from 754,000 to normal or above, according to conditions; of 61 special cases, the average was 2,406,416; as the disease progresses, the cells become polychromatophilic and show poikilocytosis; under treatment the red cells increase very rapidly, reaching or exceeding normal sometimes before the hemoglobin. In 42 treated cases with a final average of 100 per cent. hemoglobin, the red cells averaged 5,624,197. *Leukocytosis* was not met with in Porto Rico; the majority of cases showed 5000 to 10,000 leukocytes, and in chronic cases of long

standing leukopenia was often found; the average white count of 61 cases was 8009 on admission; during treatment 42 cases increased to 9041 whites, 16 cases to 7533 whites, and 3 fatal cases increased to 14,133. Leukocytosis is frequently found in hookworm cases at the Marine Hospital in Wilmington, N. C., especially in children with enlarged tonsils. The *eosinophiles* present special interest: very severe chronic cases with poor resisting power and exhausted blood-making organs have little or no eosinophilia; a rise in eosinophiles is of good prognostic import; if very severe cases, presenting little or no eosinophilia, show a fall in the eosinophile count, the prognosis is not generally good; in general, good resistance to the toxin of hookworm is expressed by eosinophilia; the "special" cases gave an average of 10.8 per cent. before treatment, and 13.2 per cent. after treatment. In 29 cases, before treatment, the differential leukocyte count averaged as follows: eosinophiles, 17.1 per cent.; polymorphonuclears, 54.5 per cent.; small lymphocytes, 16.3 per cent.; large lymphocytes, 8.6 per cent.; other leukocytes, 3.5 per cent.

Respiratory System.—The respiratory symptoms are not characteristic. Patients may complain of difficulty in breathing, especially after exertion.

Temperature.—This may be normal, subnormal, or reach 100° to 102° F. Fever at the onset is said to be a fairly constant symptom in Porto Rico. Some observers speak of a "hookworm fever."

Nervous System.—The effect upon the mental condition is marked; the infected children, of school age, are greatly handicapped by it in their studies; in severe cases, there is a noticeable delay in answering even simple questions and some of the patients are more or less stupid. From the pedagogic point of view, the hookworm inhibition to the mentality is probably the most important feature of the disease and deserves more general recognition and consideration; for instance, if a given "grade" or class in school is divided into a more advanced and a less advanced section, the majority of the hookworm cases will be found in the latter; many of the so-called "repeaters" (namely, children who have to repeat their term in a given grade) in our Southern schools are hookworm patients who, after treatment, advance more rapidly. Mental lassitude, headache, and dizziness are frequently noticed; the patients may be more timid and emotional than normal; the patellar reflex is diminished or suppressed; tingling and formication are common; either insomnia or somnolence may be marked; dizziness is common, especially upon rising suddenly to the feet; joint-pains are also very frequent.

Muscular System.—The muscles are soft and flabby, and the patient is naturally weak; he tires easily, is obliged to rest after slight exertion and a feeling of lassitude is experienced which, in absence of severe symptoms, may seem unexplained; as a result, persons who are not acquainted with the true condition attribute it in the less evident cases to laziness, and there is no doubt that much of the alleged laziness in infected districts is the natural lassitude connected with uncinariasis.

Urinary System.—The urine varies from 1.010 to 1.015 in specific gravity, is pale, neutral or alkaline, rarely acid, and is increased in amount.

Genital System.—In case of infection before puberty, delayed development may be very marked. Menstruation may be delayed several years beyond the normal and may be more or less irregular, or absent, especially in summer. This phase of the subject deserves much more serious attention by physicians than it receives. Abortions and miscarriages are frequent. Sterility and impotence are common.

Lethality.—The writer cannot state the average lethality of untreated cases in the United States, but Ashford, King, and Gutierrez (1904), after a careful study, expressed the astounding—yet probably correct—opinion that 30 per cent. of the deaths in Porto Rico were due to uncinariasis. The Porto Rico Commission reported one series of 5490 treated cases with the following results: cured 2244 cases, or 40.8 per cent.; practically cured, 377 cases, or 6.8 per cent.; improved, 1727 cases, or 31.4 per cent.; result not recorded, 522 cases; never returned, 224 cases, and ceased to return, 283 cases, total 18 per cent.; unimproved, 86 cases; died, 27 cases, or 0.5 per cent. Sandwith (1894) stated that of the patients nominally under his care, 89.5 per cent. were cured or greatly relieved, 2.5 per cent. were not relieved, 8 per cent. died.

Economic Importance.—A person who has not been in an uncinariasis district and who has not seen the extent of the cases, the way many of the people live, or rather exist, how they attempt to work, how little they accomplish compared with what they might do if they were healthy, how the mental faculties are dulled, how backward the children are, how the much-criticised country school-teachers are handicapped in their work, how exhausted the laborers become and what a change takes place in them during and after treatment, may find it difficult to grasp the full economic importance of this malady. As stated by the writer in 1902, it was “exceedingly difficult to escape the conclusion that in uncinariasis, caused by *Uncinaria americana*, we have a pathological basis as one of the most important factors in the inferior mental, physical, and financial condition of the poorer classes of the white population of the rural sand and piney-wood districts visited. This sounds like an extreme statement, but it is based upon extreme facts.” The author is thoroughly persuaded that the importance of this disease from the standpoint of the public school work and citizenship has not yet been fully grasped by any observer. The economic importance of the malady in Porto Rico, as depicted by the Porto Rican Commission, must be accepted as not being exaggerated; and as observations in the United States multiply, what once seemed an extreme opinion is now rapidly becoming a very conservative view.

The importance of the disease in the cotton mills is not to be underestimated. The typical cotton mill “anemic,” of whom the writer has seen a number, is a diagram of medium to severe uncinariasis. From a purely financial point of view, it would pay the cotton mills to compel all candidates for positions to submit to microscopic examination for diagnosis, and, if infected, also to treatment, before they are given employment. Whether the American mines will experience a repetition of the sad and expensive history European mines have had from hookworm disease, will depend upon the sanitary regulations they enforce.

Diagnosis.—In severe cases, a diagnosis upon symptoms can be made with a very high probability of correctness by anyone familiar with the disease. A positive diagnosis may be made in either of two ways: (1) Examine the feces microscopically to find the eggs; or (2) give an anthelmintic experimentally and examine the stools for the adult worms. Eggs appear in the feces 45 to 71 days after the patient becomes infected.

Blotting-paper Test.—For persons who have no microscope a very simple test may be made with filter-, blotting-, or ordinary newspaper, but there is now little excuse for this test as the States are making free microscopic examinations. Fold an ounce or so of feces in the paper and allow it to stand for several hours, then unwrap and examine for a blood stain.

Several authors who have criticised this test, seem not to have understood why it was suggested and have objected that it is open to error. Certainly it is open to error, the same as are numerous other tests, but in not a few cases it is an additional link in the evidence-chain, exactly as the anemia, the dirt-eating, the red-cell count, etc., and for the "country physician" who probably owns no microscope, and who is perhaps fifty miles away from anyone who does, it forms an additional clue. The writer has found it useful upon a number of occasions, even when a microscope was at hand, but it is self-understood that a rough test of this kind is not to be given much weight when a better test can be made, neither is a negative result with it to be accepted as final.

Treatment.¹—The usual drug in uncinariasis is either thymol or male fern, and recently beta-naphthol is springing into popularity.

Thymol.—The usual procedure is as follows: As the parasites are more or less protected by the mucus and food in the intestine, this should be removed by administering magnesium or sodium sulphate (with *abundant* water), or other purge, the evening before the anthelmintic is taken. Early the next morning (no breakfast is allowed), say at six o'clock, give (adult dose) 2 grams (30 grains) of finely powdered thymol in capsules; at eight o'clock, repeat this dose; at ten, administer another dose of salts. The size of the dose should be modified according to the age or the condition of the patient. Ashford, King, and Gutierrez, on the basis of an experience with 12,330 doses, state that in general a total, in one day, of 0.5 gram (7.5 grains) may be given with good results to children under five years; 1 gram (15 grains) between five and ten years; 2 grams (30 grains) between ten and fifteen years; 3 grams (45 grains) between fifteen and twenty years; 4 grams (60 grains) between twenty and sixty years; and 2 or 3 grams (30 to 45 grains) above sixty years. With other clinicians they warn that certain conditions, as great debility, very old age, pregnancy, advanced cardiac or other organic disease, a tendency to vomit, anasarca, chronic diarrhœa, and dysentery are unfavorable to the administration of thymol. This medication is carried on one day per week until the patient is cured. The present writer adopts the Porto Rican doses as routine, but he prefers as a precautionary measure to divide the total daily dose of thymol into three portions,

¹ For special literature on treatment, apply to Surgeon-General, U. S. Public Health Service.

administered at 6, 7, and 8 A.M. respectively; salts at 10 A.M. At the Marine Hospital, the patient is permitted coffee about 9.30 and again about 10.30. The thymol is withheld after the first or second divided dose if untoward symptoms are noticed.

It is in the interest of safety not to allow or give by mouth any alcohol, oil, or other solvents of thymol on the day of treatment.

Many authors warn about the ill effects of thymol. The Porto Rican Commission after administering 12,330 doses *seems* to incline to the view that these warnings have been exaggerated and states that, "under certain precautions," they "came to know that thymol was an exceedingly inoffensive drug." Still, they warn of certain ill effects in some cases (especially with chronic enterocolitis, œdematous patients, etc.). Nichol (1911) refers to the "serious disturbance" caused by doses totaling 90 grains per day; these observations are to the effect that the drug acts chiefly on the nerve centres; at first it stimulates, the patient is inclined to talk and laugh, the face flushes, pulse quickens, soon there follow dizziness, drowsiness, sleepiness, the pulse becomes quick and compressible, syncope appears; in more serious thymol-poisoning, somnolence passes into coma and death may ensue. In the United States there have been 12 deaths, due chiefly to following thymol with oil, or to carelessness in the precautions; one death was apparently due to the Epsom salts.

The Porto Rican Commission is entirely in harmony with the exception taken by the writer to the apparently prevailing opinion of English writers that large doses of thymol must necessarily be given. If a patient cannot stand a large dose, smaller doses will expel a few worms and thus enable him gradually to reach a condition in which the dose may be increased.

Beta-naphthol.—Bentley (1904) abandoned thymol in favor of beta-naphthol. This he has now used in several thousand cases with excellent results. The Porto Rican Commission¹ used it with success in a number of cases but later discontinued it. The drug is used in the same way as thymol, but with doses one-half as large (total of 2 grams—30 grains, instead of 4 grams—60 grains). Nichol (1911, 1912) gives beta-naphthol in larger doses (adult male dose, 90 grains; adult female dose, 75 grains; divided into 3 equal doses at 6, 8, and 10 A.M., preceded the evening before, 8 P.M., with 4 drams of magnesium sulphate, and followed at noon with 6 drams magnesium sulphate), and prefers it to thymol; he reports it as practically equally effective as the same doses of the thymol. Beta-naphthol inhibits oviposition for about five to ten days, so that the microscopic examination to test the results of treatment should not be made for at least seven days after medication.

Extract of Male Fern.—This drug has been used successfully in thousands of cases of hookworm disease. With thymol producing less serious effects than male fern, the former drug should, however, be shown pre-

¹ According to the most recent results, it is not quite so efficient as thymol; it is more necessary to thoroughly clean the intestine before using it; its systemic effects are, however, less marked, although its effects on diseased kidneys seem to be more marked.

ference. If it fails, male fern might be used. The dose is 4 to 8 cc. (about 1 to 2 fluidrams) followed by salts or calomel and salts.

Eucalyptus Oil and Chloroform.—In severe cases, especially when the patients are weak, Phillips (1905) favors the following formula: Eucalyptus oil, 2 to 2.5 cc.; chloroform, 3 to 3.5 cc.; and castor oil, 40 cc. This is divided into two or three doses, according to the age and condition, and these are given twenty to thirty minutes apart, beginning early in the morning, fasting; should any depression occur after the first dose, the later doses are omitted. Particular stress is laid on the inclusion of chloroform in the formula, as three cases in which positive diagnoses had been made, were unaffected when chloroform water was, in error, substituted. The writer has used this treatment only once and then unsuccessfully (as the patient was severely nauseated), and is not in a position to form a valid judgment on this formula.

Prevention.—Since the feces of hookworm patients represent the potential infection in concentrated form, it is clear that a proper disposal of the discharges is the greatest factor in preventing hookworm disease. Build proper privies and insist upon their being used; in mines, adopt the pail system. This one line of prevention, if carried out, is sufficient to blot hookworm disease out of existence so far as the Southern States are concerned, for fortunately we do not have to deal with any specifically identical infections in any of the domesticated animals. In countries with anthropoid apes, complete eradication is complicated by the presence of any species of ape in which either species might develop.

Numerous other preventive measures have been advanced, but while good in themselves, they fail to reach the source of the evil. The proposition to wear shoes and thus prevent ground-itch is of course a very good one, but financial considerations inhibit its universal adoption; if the infected feces are properly disposed of, ground-itch will practically disappear even if shoes are not worn. The proposition to drink boiled or filtered water is an excellent one, but of impracticable general application among the poor; but if the feces are disposed of, the danger of infecting the water is removed. To keep the hands clean is of course an excellent plan, but unfortunately one of limited application. The great principle is to prevent the dirt from becoming "dirty;" clean dirt is not dangerous.

Strongyloidosis.¹—Infection with *Strongyloides stercoralis*. — **Geographical Distribution.**—The distribution of this infection is much more general than was formerly supposed; it seems to be especially a tropical and subtropical species, but as such probably encircles the earth. American cases have been found, locally, as far north as Baltimore and imported cases even farther north. European cases have been found as far north as Belgium, England, Germany, and Holland, and the infection is also reported for Siberia. In Asia it is known for China, India, and Japan. In Africa it is known for Egypt. In South America it extends into Brazil. In general it follows the distribution of hookworms in man, and is very common in Porto Rico.

¹ SYNONYMS.—Anguilluliasis, Rhabdonemiasis. See especially Strong (1901) and Thayer (1901).

Zoölogical Distribution.—Strong (1901) reports this parasite for monkeys as well as man, and he was able to transmit the disease to monkeys by feeding infected human excreta to them.

The Parasite.—I. (a) The *parasitic* (intestinal) *adults* are parthenogenetic females, measuring 2.2 to 3 mm. long by 34 to 70 μ broad, with an œsophagus about one-fourth as long as the body; a double uterus is present, each horn containing a moderate number (3 to 6) of segmenting eggs (50 to 59 by 30 to 34 μ) which escape through the vulva, situated in the posterior third of the body. These eggs are deposited in the intestinal lumen of the host or in galleries in the intestinal mucosa made by the females, and developed into—(b) *Rhabditiform embryos*, 200 to 240 μ long by 12 μ broad, which may grow to 450 to 600 μ long by 16 to 20 μ in diameter by the time they are discharged with the feces. The buccal cavity is short, relatively broad, and without thickened chitinous lining. These embryos then develop within two or three days into—II. (c) *Free-living dioecious adults*. The *males* measure 0.7 mm. long; the tail is curved ventrally to form a hook; spicules curved, 38 μ long. The *females* measure 1 mm. long; vulva slightly posterior of equator of the body. Each female develops 30 to 40 eggs which may or may not segment in the uterus, these eggs develop forming the—(d) *Free living rhabditiform embryos*, which measure 220 μ long; when they attain 550 μ in length, they moult and at the same time change to—(e) *Filariform larvae*, possessing an elongate cylindrical œsophagus about half as long as the body. This is the infecting stage, which enters man by the mouth or through the skin, reaches the duodenum and upper part of the jejunum, and develops directly to (a) the parthenogenetic females.

Larva of *Strongyloides stercoralis* as found in fresh feces; Nerv., nervous systems; Œs., œsophagus; Int., intestines; Gen., genital primordium; An., anus. $\times 228$. (Looss.)

The complete life-cycle (a-b-c-d-e-a) is thus an alternation of a dioecious with a parthenogenetic generation (alloiogenesis) and is the cycle reported more commonly in tropical and subtropical cases. In other cases, notably in the temperate zone, an abridged cycle consisting of a-b-e-a may occur; in other words there is, in these instances, a tendency to a more completely parasitic life by the omission of the free-living dioecious generation. There must be various factors, influencing the changes in the life cycle, that are not clearly understood. Gage (1910) has found the embryos in the human lung.

Source of Infection.—Infection takes place in either of two ways, passively by means of contaminated food or drinking water, or actively through the skin.

PLATE XIII



The Kidney Worm (*Diectophyme renale*) of Man, from a Specimen in a Dog. Natural size. Original.

Frequency.—Extensive statistics of a satisfactory nature are not accessible. In general, the infection increases in frequency from cooler to warmer climates. In Washington, D. C., several cases have been known (probably none contracted within the city); the microscopic examinations in the Rockefeller hookworm campaign clearly demonstrate that the infection is much more common in this country than is generally supposed. Powell found it in 75 per cent. of the cases of anemia in India (Manson).

Duration.—The longevity of the individual worm is not established. Cases of infection are known of several years' standing, due perhaps to reinfection. Ward (1903) suggests that the very heavy infections occasionally reported possibly point to an endless chain multiplication by means of the abbreviated cycle (*a-b-e-a*) inside the intestine.

Symptoms and Pathology.—The literature contains extreme statements that the parasite is utterly harmless and that it is exceedingly injurious. A number of authors see in this parasite a worm which may indeed in some cases be apparently harmless, but which, in large numbers, may cause "clinically, an intermittent diarrhœa with intestinal disturbances, and pathologically, a catarrh of the small intestine" (Strong). At the Marine Hospital (Wilmington) we are thoroughly persuaded that the parasite may be of serious import, probably more so in white patients than in negroes.

Clinical Diagnosis.—The only possible method is by microscopic examination of the feces for the rhabditiform embryo (*b*) (see p. 286). In violent purging, eggs, strung together end on end and surrounded by a delicate tube, may appear in the stools.

Treatment.—Repeated doses of thymol as used in hookworm infection are usually advised for strongyloidosis also, but owing to the fact that parasites may burrow, treatment is reported as not always satisfactory. In the experience of the writer, thymol treatment in this disease is much less satisfactory than is usually supposed; at the Marine Hospital we have seemingly had sufficiently encouraging results with flowers of sulphur¹ to warrant the suggestion that it be given a fair trial by other men; the idea was suggested to us by a young farmer who claimed to have cured himself with this drug, after he had been unsuccessfully treated several times with thymol by several physicians; the drug (flowers of sulphur) is given in 5 to 15 grain doses (0.3 to 1 gm.) three times a day, in capsules with equal parts of sugar of milk.

Ascariasis—Eelworm Infection.—Geographical Distribution.—Cosmopolitan, more in rural districts than in cities.

Zoölogical Distribution.—In many medical works the authors maintain that the common eelworm of man occurs in certain domesticated animals, such as the pig, horse, cattle, etc. This view is not in harmony with the present zoölogical classification which recognizes these infections as generically identical but specifically distinct.

The Parasite.—*Ascaris lumbricoides* Linnaeus, 1758, is, in general terms, about as large as an ordinary lead-pencil but tapering toward

¹ The preliminary results with flowers of sulphur in amoebic dysentery and especially in flagellate diarrhœa, while not conclusive, justify a further trial.

both ends; the male measures 15 to 17, even 25 cm. in length by about 3 mm. in diameter; the female is somewhat larger, 20 to 40 cm. in length by 5 mm. in diameter, and is oviparous. The worms are grayish to reddish yellow in color; the anterior end is provided with three lips. The

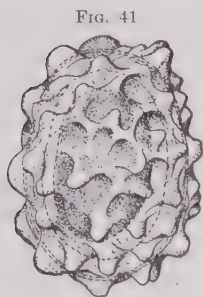


FIG. 41

Egg of the common ascaris (*Ascaris lumbricoides*) of man as found in feces. Seen with superficial focus. Greatly enlarged. (Stiles.)

egg is 50 to 75 by 36 to 55 μ , unsegmented when oviposited, and provided with a thick mammillate covering, frequently tinged yellow when found in the feces. The parasites live in the small intestine. Development is direct, without intermediate host.

Arrow-headed Eelworms.—A number of cases (10 or more) of infection with small arrow-headed eelworms have been reported for man.¹

These worms measure 40 to 90 (male) and 120 to 200 (female) mm. in length by about 1 mm. in diameter, and are easily recognizable from the arrow-shaped head; the eggs are nearly globular, 68 to 72 μ with a thinner shell than that of *A. lumbricoides*. Development is direct, without an intermediate host.

Lagochilascaris minor Leiper, 1909. —This ascaris, provided with three lips and three intermediate lips, has been reported in two cases of subcutaneous abscess at Trinidad.

(?*Ascaris*) *maritima* Leuckart, 1876, has been reported for man but once in Greenland. One immature specimen was vomited by a child and was doubtless an accidental parasite, possibly swallowed with the entrails of some food animal.

(?*Ascaris*) *texana* Smith and Goeth, 1904, has been described as a new eelworm for man in Texas; measure 58 to 60 mm. in length and is said to possess intermediate lips; uterine eggs segmented, 60 by 40 μ . Through the kindness of the describer, Allen J. Smith, the writer was enabled to examine the original specimens; the structures described as intermediate lips do not correspond to the intermediate lips so far as he is familiar with them in other species of *Ascaris*, but as the material was poor the writer refrains from expressing any definite opinion regarding this species, which is still *sub judice*.

Ascaris sp. incert, is reported by Wellmann, 1905, for Angola.

Source of Infection.—The egg escapes in the feces and slowly (in one to several months, according to conditions) develops an embryo; no

¹ These parasites have been variously classified as *Ascaris canis*, *A. marginata*, *A. mystax*, etc., and it has been assumed by some authors that these all represent one species. More recent study has persuaded helminthologists that the worms of this group should be separated into several species distributed over several genera. It would be difficult to determine definitely, without a reexamination of the actual specimens, to which species the worms of the earlier cases in man belong, but in all future cases the following genera and species in particular should be taken into consideration: *Belascaris mystax* (Zeder, 1800), an eelworm of cats; *Toxascaris canis* (Werner, 1782), the common eelworm of dogs; *Toxascaris limbata* of cats and man. Authors are not yet entirely in harmony as to the nomenclature of this group, but the types are as follows: *Belascaris*, 1907 (*mystax*); *Toxascaris*, 1907 (*leonina*); *Toxocara*, 1905 (*canis* Werner).

intermediate host is required at least for *Ascaris lumbricoides* and *Toxocara canis*; but when the developed eggs are swallowed, either in contaminated food or water, or from hands soiled with dirt containing the eggs, the embryo develops directly to the adult stage. Drinking water and fruits, especially, are blamed for carrying the parasite to man. Some years ago the writer bred common house-flies in a dish containing eggs of the eelworm of hogs, a parasite very closely allied to that of man, and later found the eggs in the intestine of the adult flies. It would seem, therefore, that flies, by breeding in privies, might act as disseminators of the lumbricoid worm of man.

Frequency.—The eelworm is one of the most common parasites of man; it may occur at any age, from about eight months to eighty-five years, but is usually more frequent in childhood (from five to ten years) and youth than in adult age, and more common in women than in men. Autopsy statistics for Germany published by Heller and Müller give the following combined results: males, 220 cases in 2275 autopsies, or 9.67 per cent.; females, 194 cases in 1446 autopsies, or 13.41 per cent.; children, 101 cases in 584 autopsies, or 17.29 per cent. It was present in 0.49 per cent. of 3457 persons examined under direction of the writer. In Porto Rico, Guam, and the Philippines it is excessively common.

Usually only from 2 to 6 individuals are present in one patient, but infections with 30, 40, 100, 140, and 300 to 600 worms are recorded, while Fauconneau-Dufresne (1880*a*) reports the case of a boy of twelve years who passed (chiefly by vomiting) more than 5000 worms within less than three years, 600 being passed in one day.

In general terms *Ascaris lumbricoides* is more common in warmer than in temperate and colder climates, and more common in the rural districts than in the cities. Authors attribute its greater frequency in rural patients to the use of unfiltered water, but other factors seem to be of more importance: in cities with a sewage system the infectious material is carried away, while in country districts the surface privy affords greater possibilities for the spread of infection.

Duration.—The worm matures and oviposits in about a month after infection, but definite details as to the longevity of the individual parasites are lacking.

Symptoms.—Very frequently no symptoms are noticed. In other cases they are more or less indefinite, practically all of the symptoms reported for teniasis and oxyuriasis being recorded for ascariasis also. For instance, among those recorded may be mentioned the following: irritation of the skin, urticaria, pallid appearance, alternate pallor and redness of the face, jaundice, dark rings around the eyes, unequal or dilated pupils, flashes before the eyes, mydriasis, amblyopia, amaurosis, strabismus, disturbances in sight and hearing, inflammation of the eye, itching of and picking at the nose, grinding of the teeth, bad taste and offensive breath, dry cough, hiccough, aphonia, anorexia, irregular or capricious appetite, dirt-eating, eructations, sensibility of stomach on pressure, nausea, vomiting, gastrorrhagia, vague abdominal pain, borborygmi, colicky pains, cramps, irregular bowels, diarrhoea, constipation, intestinal obstruction, meteorism, itching at the anus, muscular

pains, progressive emaciation, headache, vertigo, fretfulness, fainting spells, chorea, convulsions, epilepsy, catalepsy, ecstasy, hysterical conditions, eclampsia, neuralgia, paralysis, psychoses, tetanoid states, pseudomeningitis, palpitation and irregular action of the heart, syncope, etc.

While many physicians recognize elements of danger in an infection with ascaris, others sometimes view eelworms with little more than a passing curiosity. Hundreds of cases of ascariasis, recognized or unrecognized, may pass through a physician's hands without any fatal results being noticed. Still, the occasional danger connected with eelworms is deserving of attention. If a light infection is present, the chances are very great that nothing serious will result from it; but unfortunately these worms have a habit of wandering, especially in febrile conditions, and medical literature shows that these wanderings, even in light infections, present a dangerous aspect of the disease. The escape of erratic eelworms by the mouth or nose is not very rare. If during this wandering the worm comes into contact with an ulcer, perforation into the abdominal cavity or the lungs may result; or the worm may enter the Eustachian tube and escape by the external ear; in some cases it enters the lacrimal duct; or it may turn at the larynx and pass a greater or less distance down the trachea and bronchi, in some cases causing suffocation, in others abscess or gangrene of the lungs; about 40 cases are recorded in which ascarids have entered the air passages. About 90 cases are recorded in which the eelworms have wandered into the bile ducts, 9 cases into the pancreatic duct, and some 20 cases into the urinary passages. In some cases the worms pass into the abdominal cavity, either piercing the intestinal wall or working their way through an ulcer. Blanchard has compiled 81 cases in which eelworms have escaped through the body wall; 29 cases through the umbilicus, 30 through the groin, 10 at unstated points of the abdomen, 2 by the hypochondrium, 2 by the lumbar region, 2 by an inguinal abscess, 1 each by the sacral, pubic, and perineal region, and abscess of the thigh, inferior portion of thorax and linea alba. Davaine points out that, corresponding to hernia, ascarids escape by the umbilicus more frequently in children than in adults, and by the groin more frequently in adults than in children.

In view of the foregoing brief account of erratic ascarids, in not a few cases fatal, it is seen that it is at least worth while, from a prophylactic standpoint, to treat all cases which are found, even independently of the question as to whether any moderate or serious local or perhaps reflex symptoms are traced to the presence of the worms in the patient under consideration. That heavy ascarid infections, such as are found in unhygienic tropical countries, may be of considerable clinical importance is evident. Such cases may be easily subject to an erroneous diagnosis of uncinariasis.

Diagnosis.—It is possible to make a diagnosis independently of symptoms, either by a microscopic examination of the feces to find the characteristic eggs, or by recognition of worms passed.

Treatment.—Santonin is the classical drug for ascariasis. It is given in powder or troches; dose 0.01 gram per day ($\frac{1}{6}$ grain) for each year of

the child's age, 0.06 to 0.3 gram (1 to 5 grains) for an adult. It is best given with an equal or greater amount of calomel, every morning two or three days in succession; then repeat the medication every three or four days as long as eggs are found in the feces or until no further worms are expelled. In treating children it is well to forewarn the mothers of the possible effects of *santonin* upon the patient.

Among other drugs used for the expulsion of eelworms may be mentioned: oil of *chenopodium*, 0.13 to 0.6 cc. (2 to 10 minims) on a lump of sugar or in emulsion, before meals for two days, followed by a purge (calomel). Fluidextract of *senna*, with equal parts of fluidextract of *spigelia*, 2 to 4 cc. ($\frac{1}{2}$ to 1 dram) of the mixture, three times daily until purgation occurs. *Thymol* is sometimes recommended, but at the Marine Hospital in Wilmington it has not given satisfactory results.

Serious intestinal obstruction by *ascarids* should be treated as obstruction from any other cause.

Oxyuriasis.—Pinworm Infection.—Geographical Distribution.—Cosmopolitan.

Zoölogical Distribution.—The pinworm of man is not known to occur in any other animal; generically identical but specifically distinct infections are, however, known for a number of mammals.

The Parasite.—*Oxyuris (Oxyurias) vermicularis*¹ (Linnaeus, 1758), known as the pinworm, seatworm, also mawworm, is a small, white, roundworm measuring 3 to 5 mm. (male) to 10 mm. (female) in length, 0.16 to 0.6 mm. in diameter; the male has but one spicule; the female is provided with a relatively long, sharply pointed tail; the vulva is in the latter half of the anterior third of the body; two uteri are present filled with numerous eggs, in which an embryo is developed before oviposition; these eggs are 50 to 52 by 16 to 24 μ , with thin shell, and with dorsal surface much more convex than the ventral. The earlier stages of the parasite live in the small intestine, where the worms copulate. The males are not long-lived. The fertilized females wander to the cecum, and later when gravid to the colon. It has been maintained that the normal location for pinworms is the vermiform appendix; it cannot be doubted that pinworms do enter the appendix, for Heller, for instance, reported 36 males in 1 case: 19 males and 19 females in another; 30 males and 9 females in another; 46 males and 27 females in another; and more recently pinworms have been incriminated as possible exciting cause in certain cases of appendicitis; Railliet (1911) reported it in 59 cases (=48.7 per cent.) of 119 inflamed appendices; but it hardly seems proved that the appendix is the normal habitat for these parasites. The statement occasionally found in medical works that the embryo escapes from eggs oviposited in the

FIG. 42



Embryo of the common pinworm (*Oxyuris vermicularis*) of man, in the egg-shell, as found in fresh feces. (Leuckart.)

¹ SYNONYMS.—*Ascaris vermicularis* Linnaeus, 1758; *Oxyuris vermicularis* (Linnaeus) Bremser, 1819; *Trichina cystica* Salisbury, 1858; *Filaria cystica* (Salisbury) Railliet, 1893, in part only (not *F. cystica* Rudolphi, 1819).

rectum and develops there into an adult is possibly traceable to Vix (1860); but this view cannot be accepted.

Source of Infection.—Pinworms have a pronounced tendency to wander out of the anus, and when the female is crushed by scratching with the fingers, to relieve the irritation, a person infects his fingers, especially under the finger nails, with the embryo-containing eggs; from the fingers to the mouth or nose is but a short distance, and auto-infection thus occurs. Or the embryos in the bedclothes may easily soil the hands of a bed-fellow, a companion, or a nurse, and thus be transmitted to a second person. Or the eggs (free in the feces or in the body of the discharged female worms) may be transmitted to people by means of contaminated food. No intermediate host is necessary. Theoretically it seems perfectly possible that flies may occasionally, if not frequently, play a role in the dissemination of the eggs.

Frequency.—This parasite is one of the most common of the intestinal worms. It is more frequent in children (from three to ten years) and women, but has been observed in babes of five weeks up to men of eighty years. It was found in 1.3 per cent. of 3457 persons examined under the writer's direction at the Hygienic Laboratory at Washington. Heller reports it in the proportion of 33.8 per cent. for children, 21.1 per cent. for women, and 18.8 per cent. for men, in 611 autopsies at Kiel, Germany. Infections are reported as more common in the spring than at other seasons of the year. The number of specimens of pinworms in one person varies from a few to such heavy infections that the mucosa of the large intestine may be covered with them.

Duration.—While the longevity of the males appears to be rather limited, that of the individual female is not established. Cases of infection of ten to fifteen years and even much longer are recorded, but these are perhaps due to repeated auto-infection.

Symptoms.—Doubtless many cases of light infection pass unnoticed, and in case the person is of clean personal habits, the infection dies out. In heavy infections, however, there may be marked irritation of the intestinal mucosa, resulting in a catarrhal condition and a diarrhœa; there may be foul breath, nausea, vomiting, abdominal pain, tenesmus, deep rings around the eyes; further, one may find headache, restlessness, sleeplessness, itching at the nose, vertigo, unequal pupils, chorea, and even convulsions. One of the most constant symptoms is an intense itching and burning at the anus, due to the wandering of the female, especially shortly after the patient retires; the anus appears red, irritated, sometimes bloody; reaching the perineum the worms may pass to the vagina if the skin is moist, and may here cause hyperemia, increased secretion of mucus, and sometimes hyperesthesia and leucorrhœa; sexual excitement may result. Wandering pinworms have been found in the vagina, uterus, and even in the abdominal cavity.

Diagnosis.—While symptoms may indicate pinworm infection, a positive diagnosis may be made in several different ways: the adult worms may be found in the stools, occasionally in considerable numbers; or they may be found in the crotch, especially if the child is examined during the restless period after retiring; a microscopic examination of

scrapings around the anus (taken with a clean dull knife or a microscopic slide or other suitable object), or the cleanings from the finger nails may reveal the characteristic eggs; finally, the eggs may be discovered by a microscopic examination of the feces. Opinions are divided regarding the value of the last; some authors consider that the eggs are not found free in the stools, while others state that they are common. The writer's experience is that the eggs may be found in fecal examinations even in some cases in which pinworm infection is not even suspected; a negative examination is not of much value.

Treatment.—This should take into consideration two distinct points: namely, not only the removal of the gravid female pinworms from the rectum, but also the removal of the younger worms from the small intestine. A failure to consider this latter point doubtless explains not a few cases of treatment which have not met with success. For removing the younger pinworms from the small intestine, several drugs may be used, as santonin and calomel (of each 0.05 to 0.1 gram— $\frac{3}{4}$ to $1\frac{1}{2}$ grains) given several days in succession, or large potions of an infusion of gentian, or active saline cathartics repeated several days in succession, or thymol or beta-naphthol. Ungar gives immediately after a laxative, four doses per day of naphthalin (0.1 to 0.4 gram—2 to 6 grains) according to age, for two or three days in succession between meals.

To expel the gravid females from the rectum, rectal injections are used. An infusion of quassia seems to be one of the most popular remedies. Other commonly used enemata are: lime-water, salt and water, iced water, salt and milk (highly spoken of), cold water, aloes, diluted vinegar (which should be sterilized before using, otherwise the patient may become infected with vinegar-eels), perchloride of iron, glycerin, benzine (20 drops to a pint of warm water), finely chopped garlic with water (which has stood for twelve hours and is then strained through linen). Diluted carbolic enemata are advised by a number of authors, but they do not seem to have any special advantage over the other drugs and have in some cases decidedly poisonous effects.

The injections are given with the buttocks elevated, or in the knee-chest position, at first every evening, then every two or three or four evenings, until all evidence of worms has disappeared. If too large an injection is given to be retained this washes out a number of worms; but it should be followed by a small injection, two to four ounces, or an amount which can be conveniently held.

Ointments of various kinds may be applied to the anus and perineum to relieve the itching.

Physaloptera caucasica Linstow, 1902, has been reported but once for the intestine, in Caucasus. (Length 14 [male] to 27 [female] mm., breadth 0.71 to 1.14 mm. Eggs 57 by 39μ .)

Physaloptera mordens Leiper is reported from the oesophagus, stomach, small intestine, and liver of natives in tropical Africa (Quilimanar, Uganda), and it also occurs in *Simia*. The male worms measure 30 to 50 mm. long, the females 40 to 55 mm. long by 2 to 3 mm. broad; the males have unequal spicules, 4.6 and 0.6 mm. long and a pair of caudo-lateral cuticular expansions (bursa) provided with paired pedunculated

papillæ in addition to the more median-situated sessile papillæ on the body; eggs 43 by 35 μ . These worms may be easily mistaken for young specimens of *Ascaris*, but they have two lips instead of three.

Œsophagostomum.—This genus contains worms that might at first sight be mistaken for hookworms, but the head is straight; the mouth is provided with a chitinous ring, followed by a cuticular swelling interrupted ventrally by a transverse constriction. Three different worms of this genus have been described as parasites of man, namely:

Œsophagostomum brumpti Railliet and Henry, 1905, in a tumor of the colon, in a Pouna negro on the Omo River, Africa. Females, 8.5 to 10.2 mm. long by 0.295 to 0.325 mm. in diameter; vulva 0.35 to 0.495 mm. from tip of tail and cephalad of anus.

Œsophagostomum apiostomum (Willach, 1891), larva in hemorrhagic cysts in wall, adult in lumen, of colon and cecum, of a negro in Nigeria. It was first reported from a monkey (*Macacus cynomolgus*). The male measures 8 mm., the female 10 mm., long.

Œsophagostomum stephanostomum thomasi Railliet and Henry, 1909, larva in nodosities of intestinal wall, in Amazon, Brazil.

Ternidens deminutus (Railliet and Henry, 1905) was described from specimens which were probably the original worms in Monestier's (1867 *a*) paper on chloro-anemia in a Makouan negro at Mayotte; Monestier thought they were hookworms. The head is straight, the mouth terminal and surrounded with a fringed collar of 22 rounded lamellæ; male 9.5 mm. long, spicules 0.9 mm. long; female 14 to 16 mm. long, vulva preanal, 0.68 mm. from tip of tail. Turner (1910) reports this species in natives from Nyassal, and it is also reported for *Macacus sinicus* of India and *Macacus cynomolgus* of Saigon.

Strongylus gibsoni Stephens, 1909, is recorded in the feces of a Chinese at Hongkong.

Haemonchus contortus (Rudolphi, 1803) is an exceedingly common parasite in the stomach of cattle, goats, and sheep. It is reported once (Magalhães, 1908) in a man, in Santa Vitoria, Argentine, who exhibited symptoms of uncinariasis.

Trichostrongylus Looss, 1905.—Three small intestinal nematode worms (*T. vitrinus*, *T. probolurus*, and *T. instabilis*¹) have been reported for man in Egypt, and one of them (*T. instabilis*) for man in Japan. They do not seem to be important parasites, and their normal habitat seems to be other animals (sheep, antelope, dromedary, baboon) rather than man. They measure 4 to 6 or 7 mm. in length. Their eggs might be mistaken for hookworm eggs, but are in general somewhat larger, 73 to 90 μ long and are oviposited in the 8 to 32 cell stage.

Anguillulina putrefaciens (Kühn, 1897).—Small nematodes of various sorts frequently gain access to the stomach by being swallowed accidentally with food (vegetables, vinegar, water, etc.), and are likely to appear either in the vomit or in the feces. As an example of this sort

¹ SYNONYMS.—*Strongylus instabilis* Railliet, 1893 *a*; *S. subtilis* Looss, 1895; *Trichostrongylus subtilis* (Looss, 1895) Looss, 1905; *Tr. instabilis* (Railliet, 1893) Looss, 1905 (also *Tr. colubriiformis* [Giles, 1892] *teste* Lane). See also Stiles, 1902 *t*, 41 to 42, Figs. 14 to 21.

reference may be made to *Anguillulina putrefaciens* reported by Botkin (1883) as *Trichina contorta*, in the vomit. The worms gained access to the stomach in onions and caused vomiting.

Rhabditis sp. has been reported in the washings from the stomach (Trese, 1907).

Trichocephaliasis.—**Whipworm Infection.**—**Geographical Distribution.**—Probably cosmopolitan.

Zoölogical Distribution.—The whipworm of man is also said to occur in various apes and lemurs; generically identical but specifically distinct infections are more or less common in dogs, cattle, sheep, and a number of other animals.

The Parasite.—*Trichuris trichiura*¹ (Linnaeus, 1761), the whipworm, has the general form of a whip, the posterior swollen body representing the handle, and the lash representing the slender filiform anterior portion. The male measures 40 to 45 mm., the female 45 to 50 mm. in length. The parasites inhabit the cecum, but are occasionally found in the vermiform appendix and in the colon, rarely in the small intestine. They produce numerous characteristic eggs, 50 to 54 by 21 to 23 μ , of a yellowish to dark brown color, with unsegmented protoplasm and with a peculiar light spot at each pole resembling apertures.

Source of Infection.—The eggs develop after being discharged in the feces, and with the contained embryo are swallowed in drinking-water or contaminated food. An intermediate host is not necessary.

Frequency.—This is one of the most common parasites of man, varying in frequency from less than 1 per cent. up to 90 per cent. of persons examined in different parts of the world. In general terms it is more common in warmer than in colder climates. In Washington, according to examinations made under the writer's direction, it is twice as common in colored as in white children; it was present in 7.69 per cent. of 3457 persons examined by the Zoölogical Division of the Public Health and Marine Hospital Service; it may vary greatly in frequency in different wards of the same asylum; in the United States Government Hospital for the Insane 10.8 per cent. of 500 white male patients were infected, the highest percentage being 38.98 in soldiers returned from the Philippines. It is most frequent in children from three to ten years of age.

Duration.—The length of life of the individual parasite is not established.

Symptomatology and Pathology.—The medical opinions expressed regarding this worm have been too frequently characterized by extreme statements, varying from the view that it is of no medical importance whatever, to the view that it is the cause of very serious disease. That, in the vast majority of cases, it is of scarcely any appreciable importance, and that its presence cannot be recognized symptomatically may be

FIG. 43



Egg of whipworm. \times
400 (Looss)

¹ SYNONYMS.—*Trichuris* Büttner, 1761; *Ascaris trichiura* Linnaeus, 1771; *Trichocephalus hominis* Schrank, 1788; *Trichocephalus dispar* Rudolphi, 1801.

conservatively admitted. But that severe infections do not produce injury is not in accordance either with probability or with recorded observations. According to some observers, the worm simply lies loose on the intestinal mucosa; but other equally competent observers report finding it with its head burrowed in the epithelium. Askanazy reports hemoglobin in the worm's intestine, and several cases of severe anemia have been recorded, which were apparently justly attributed to heavy infections with whipworms. Andrikidis (1906) refers to digestive and nervous symptoms and anemia, and says there may be a picture of recurrent appendicitis.

Guiart, of Paris, has suggested that the wounds made by whipworms form the point of entrance for the typhoid bacillus. Examinations made at Washington do not bear out this hypothesis for this locality. Of 200 typhoid patients examined by the author (1907), 92.5 per cent. failed to show any intestinal worms, and the whipworm infection found was only very slightly above that of the normal population.

Clinical Diagnosis.—The only method is by microscopic examination of the feces for the characteristic eggs.

Treatment.—Medical writers agree that treatment is unsatisfactory. Thymol is recommended by some, but in laboratory experiments on the dog, Pfender and the writer have found it worthless in whipworm infections. In the literature on hookworm disease, frequent mention is found of the expulsion of whipworms by male fern administered in treating uncinariasis. Hemmeter (1902) advises irrigation of the colon with benzine (1 dram of benzine to 1 quart of warm water) and at the same time internal administration of benzine.

Prevention.—A proper disposal of the alvine discharges is of first importance. Personal cleanliness, the use of proper drinking-water, and the disuse of surface-water for drinking purposes will also contribute largely to prevention.

Infection with Mermithidae.—These infections are of little significance. At least one recorded as filarial in nature probably belongs here.

(? *Filaria*) *hominis oris* Leidy, 1850, has been reported once "from the mouth of a child;" it measured 5 inches, 7 lines long, by $\frac{1}{8.4}$ of an inch in diameter. Nothing is known of its anatomy. It seems very possible that this may have been a *Mermis* obtained in eating an apple.

Infection with Gordiacea.¹—A number of different horse-hair worms are reported as accidental intestinal parasites in the intestine of man. They are, however, rare and their effect temporary. Six cases are known for North America; in 4 of these the parasite was *Paragordius varius*. Other species reported for man are: *P. tricuspidatus*, *P. cinctus*, *Gordius aquaticus*, *G. chilensis*, *Parachordodes alpestris*, *P. pustulosus*, *P. tolosanus*, and *P. violaceus*.

Infection with Thorn-headed Worms (Acanthocephali).—The thorn-headed worms differ from the nematodes in two chief characters: namely, in the absence of an intestine and in the presence of a retractile rostellum armed with hooks. An intermediate host (insects of various kinds)

¹ For zoölogical characters and a compilation of cases, see Stiles, 1907 c, *Bull. No. 34*, Hygienic Laboratory.

is required for their life-cycle. This group of parasites is of very little known importance in human medicine, but of greater importance in comparative medicine. Three species have been recorded as intestinal parasites of man, namely:

Gigantorhynchus hirudinaceus (*Echinorhynchus gigas*)¹ 10 to 50 cm. long; eggs 80 by 100 μ long, with three shells; very common in hogs; May-beetles and June-bugs are the intermediate host; alleged to occur in man in South Russia.

*Gigantorhynchus moniliformis*² (Bremser, 1819), 4 to 8 cm. long; eggs 85 to 45 μ ; occurs in rats and certain other rodents; it is also reported for the dog; a beetle (*Blaps mucronata*) is the intermediate host; raised in man experimentally by Grassi and Callandruccio (1888c). According to Magalhães, the large roach (*Periplaneta americana*) may also serve as intermediate host and Sewart (1912) states that in Algiers the common cock-roach plays this role.

Echinorhynchus hominis (Lambl, 1859), a doubtful species, 5.6 mm. long, reported but once.

In all these infections, except with *Mermithidae*, the diagnosis should be made by microscopic examination of the feces to find the eggs. Treatment is the same as for *Ascaris*.

INTESTINAL AND MUSCULAR ROUNDWORMS

Trichinosis or Trichiniasis.—Infection with *Trichinella spiralis*.³

Geographical Distribution.—Trichinae are practically cosmopolitan, because of the wandering of rats; but trichinosis as a recognizable disease in man is practically limited to persons who indulge in the mis-custom ("Unsitte") of eating raw or rare pork.

Zoological Distribution.—From a practical, hygienic point of view, the zoological distribution of trichinosis extends to man, hogs, wild boars, rats, dogs, and cats. It is also reported for several other animals, such as the fox, etc., and has been transferred experimentally to several rodents (rabbits, hares, etc.) and other animals (sheep, cattle, etc.), but these exceptional infections or infections in animals not used for food do not enter largely into any scheme of prophylaxis.

The Parasite.—Three stages of the parasite should be held in mind:

(a) The *adults* live in the duodenum and jejunum; the males measure 1.4 to 1.6 mm. in length by 40 μ in diameter, while the females are 3 to 4 mm. long by 60 μ thick; they are circular on cross-section and appear as minute thread-like objects; the *oesophagus* is supported by a single row of cells known as the *cell-body*; the male is without spicules; the female is *viviparous*, the vulva being situated about one-fifth the length of the body from the mouth. The males die shortly after copulation. The

¹ SYNONYMS.—*Taenia hirudinacea* Pallas, 1781; *Echinorhynchus gigas* Goeze, 1782.

² SYNONYMS.—*Echinorhynchus moniliformis* Bremser, 1819.

³ While the more commonly known name *Trichina spiralis* is not available for this parasite, it is not quite certain whether its correct name is *Trichinella spiralis* or *Trichinus spiralis*.

females may remain for a few weeks in the lumen of the intestine, or they bore into the lymphatic spaces of the intestine where they live about five to seven to twelve weeks and deposit their numerous young, about 1500 or more per female, namely, the—

(b) *Embryos*, which measure about 90 to 100 μ in length by 6 μ in breadth; these wander, either with the lymph, or with the blood, less frequently actively, to the striated muscles. They begin to reach the muscle about the tenth day after infection; they enter the muscle fibers and there develop into the—

(c) *Encysted Larvæ*.—The cysts vary somewhat in size, but are usually about 400 by 250 μ . These encysted larvæ may remain alive in the muscles for years, cases being reported for as long periods as twenty to thirty-one years. The encysted worm (the “fleshworm”) is the infecting stage, found in the hog; upon being swallowed in raw or rare pork, the cyst is destroyed, the larvæ pass from the stomach to the small intestine and develop within about two days or less to the adults; the latter copulate and may have embryos in the uterus within less than a week after infection.

Source of Infection.—Leaving out of consideration the rare exceptions, and considering only the usual methods, it may be said that (a) *man* obtains trichinosis from eating pork; (b) *hogs* become infected from eating (1) uncooked swill containing scraps of pork, (2) swine offal at country slaughter-houses, and (3) rats; (c) *rats* obtain their infection by eating (1) each other, (2) scraps of pork in houses or at meat-shops, and (3) swine offal at country slaughter-houses. Thus, rats alone, swine alone, or rats and swine together, may keep up an endless-chain infection, while the infection which reaches man terminates with the death of the individual. Accordingly, man must be viewed as a more or less accidental host, while the rat, because of its cannibalistic habits, presents, theoretically, ideal conditions to serve as a normal host.

Duration.—As a clinical combination of symptoms, trichinosis may last from a few days to several months, but usually it runs its course in about two or three to five or seven weeks; convalescence is slow and may require ten to seventeen weeks, while cases are recorded where the patients have not fully recovered from the effects for years. As an infection, on the other hand, it is reported as having lasted from five to twelve years in man and eleven to twenty-four years in the hog;¹ that is, cases are reported in which it is maintained that the encysted parasites have retained their vitality for these periods.

Symptoms.—Incubation may last from several hours to several weeks, according to the amount of infection, and according to whether a large number of parasites are ingested at one time, or whether consecutive infections of a smaller number of worms have occurred. Some infections are so light as to be entirely overlooked; other light cases, which might escape proper diagnosis, are recognized because of their contemporaneous occurrence with severe cases in the same family or among people trading with the same butcher. The more severe typical cases present

¹ It is not altogether clear that this record for the hog must be accepted as absolute, for repeated infections might have occurred during these long periods.

Rupprecht's three more or less well-defined periods, corresponding to the three stages of the parasite and their respective location:

1. *Period of Ingression.* The adult parasites are in the lumen or the tissues of the intestinal tract, hence the gastro-intestinal symptoms predominate; but in some cases these may be absent or very slight. Within a few hours to two days or so, there is a more or less heavy feeling in the stomach, with eructations; nausea develops, and the patient may vomit once or several times, or in some cases persistently for some days; the appetite is diminished, constipation, or more generally diarrhœa, occurs, often with colic; the stools are at first fecaloid, but become looser even to an almost watery consistency; this diarrhœa may continue for some weeks or may give place to a more or less obstinate constipation. Muscular pains may develop early, even before the muscular tissue is invaded by the parasites; recurrent abdominal pains, especially at night, and as frequently as six attacks within twenty-four hours, may develop in the severest cases; the extremities become cold; the pulse small and intermittent. Toward the eighth day a temporary first œdema of the eyelids and face may appear lasting for from two to five days. From the seventh or eighth day on, large numbers of wandering embryos are found in the peritoneal, pleural, and pericardial cavities.

2. *Period of Digression.*—This begins on about the ninth or tenth or fourteenth day, rarely as late as the forty-second day (repeated small infections?), and corresponds to the period during which the embryos are wandering and attacking the muscles; accordingly muscular symptoms (myositis) are the most prominent. The symptoms may be exceedingly light to severe. Certain muscles, particularly the biceps and gastrocnemius, are more firm than usual, hard and very tender, especially when the patient extends the forearm or leg. Movement may cause excruciating pain, and for relief the patient assumes a position of semi-flexion. Mastication, speech, and movement of the eyes become painful; more or less complete aphonia may occur and the eyes become fixed; respiration becomes difficult, and respiratory troubles are likely to be severe, especially in the fourth and fifth weeks; there may be severe dyspnoea, accompanied by violent asthma.

3. *Period of Regression.*—All symptoms become exaggerated, and in addition the patient falls into an extreme cachexia; a second œdema develops about the twenty-fourth day, occurring in about 90 per cent. of the cases and attacking the head especially; hence the name, "disease of the big head," occasionally applied to trichinosis in Europe. The larval parasites encyst and the patient gradually recovers.

This rather diagrammatic clinical picture varies according to the amount and number of the infections. Early or late pruritus and formication may occur at certain points or over the entire body; cutaneous anesthesia is rare. Profuse sweating is likely to occur, especially during the myositis. Stiffness of the muscles of the neck and back, extending to a distinct opisthotonos, has been recorded. Thirst is increased. In females, anomalies occur in menstruation, and abortion is reported for some pregnant patients.

The urine decreases in quantity with the second week, but toward the

fifth or sixth week and in convalescence there is polyuria. There may be an abundant sediment but the presence of *albumin is exceptional*; the urine may be intensely red in color.

As the nutrition is poor, extreme emaciation and anemia may develop, and there may be œdema of the lungs and an obstinate bronchitis. The mental faculties are dulled, and the patient is indifferent to what occurs in his presence. In severe cases more marked nervous symptoms develop—extreme insomnia or somnolence, delirium, etc. Opisthotonos, due to stiffness of the muscles of the neck and back, may be noticed. Even in light cases moderate *fever* may be present; in severe cases it appears during the stage of ingression; the temperature rises after the beginning of the muscular symptoms, often reaching 104° F., or even 105.8° F., its duration (two or three to five or six weeks) depending upon the severity of the infection; it may be remittent or intermittent. The *pulse* follows the temperature; in high fever it may exceed 100 and be extremely feeble. The skin not infrequently shows a miliary or roseolous eruption, more rarely herpes, and the œdema is frequently followed by extensive epidermic desquamation.

Lethality.—The death-rate in different outbreaks varies between 0 and 100 per cent. Of 14,820 cases in Germany which were collected by the writer for the years 1860–97, 831 were fatal, giving a death-rate of 5.6 per cent. The death-rate is low before the second and after the seventh week, and highest from the fourth to the sixth week, when the myositis is at its maximum.

Diagnosis.—In its severe form, trichinosis is a disease which occurs in groups of cases. In less extreme outbreaks cases may be mistaken for typhoid fever and “muscular rheumatism.” The possibility of trichinosis should always be held in mind in case of the occurrence of several typhoid-like attacks in the same family or neighborhood, or among friends (especially Germans), and following a celebration at which pork was served, or among families trading with the same butcher. When trichinosis is suspected make the following examinations:

(a) Of the pork (if any has been left) to find encysted larvæ; if these be found, chop the pork finely, wash thoroughly in water to remove the salt, and feed immediately to two or three rabbits, guinea-pigs, or white rats in order to determine whether the larvæ are alive; never use wild rats or mice for this experiment; kill one animal after two or three days and examine the contents of the upper half of the small intestine for the adult worms; kill the second animal after two weeks, the third after three weeks, and examine the muscular portion of the diaphragm for the larvæ. Even if live trichinæ are found in the intestine of the first animal, an examination of the second and third experiment animals may show that the parasites were too weak to reproduce to any extent, hence the prognosis is favorable.

(b) Upon the first suspicion of trichinosis, the patient's stools should be examined for discharged adult worms, especially if the diarrhœa is severe; dilute the fecal matter with warm water, using a rather tall, narrow graduate, or similar dish; shake well and allow the worms to settle to the bottom; pour off any matter which floats; place the sediment

in a shallow glass dish so that it will not be over one-twelfth of an inch deep, and, moving it gently over a dark background, by tipping the dish first to one side and then to the other, hunt for small hair-like objects which tend to cling to the glass (if the tipping is not too rapid); place these, if found, in a drop of water on a slide, cover with a cover-slip, and examine under a low-power lens.

(c) Examine the patient's blood for eosinophilia. The observations by Brown of the enormous increase in the eosinophiles has led to the recognition of many sporadic cases which otherwise would have been overlooked.

(d) If in the third week or later and a diagnosis is not established but trichinosis is suspected, excise a minute piece of the patient's deltoid; tease this on a slide, add a drop of water, or water and glycerin, flatten gently by pressure on the cover-glass, and examine under low power.

Prognosis.—This is better in children than in adults, better in cases with severe diarrhœa in the early part of the disease, and good after the seventh week. If appetite, sleep, and respiration remain good, prognosis is good. Coma, delirium, and, in the last weeks, elevation of temperature and extreme dyspnœa are bad prognostic signs. Some recover in a few weeks; in others recovery is tedious, requiring months or several years.

Treatment.—If from the occurrence of a group of cases, or from a microscopic examination of meat, an early diagnosis is made, the stomach should be washed out immediately. In case of an early diagnosis, but at a time too late to recover the ingested undigested pork or the worms from the stomach, purge the patient with calomel, in order to remove as many of the worms as possible, for each female removed from the intestine means a reduction of the muscular infection by from 1500 to several thousand worms. Calomel has in addition some anthelmintic property. Thymol or beta-naphthol might be administered with good effect. Unfortunately the administration of anthelmintics has not been followed by very satisfactory results, the failure being due at least in part to the subepithelial position of the females. No drug is known to kill the parasites in the muscles. After the parasites once leave the lumen of the intestine, all treatment must be symptomatic and supportive. Hot baths and morphine may be used to relieve pain; the profuse perspiration is relieved by atropine.

Prevention.—The German school favors a microscopic examination of pork before it is placed on sale, but statistics (Stiles, 1901) show that this system is not only very expensive but also open to many practical sources of error. Frequent suggestions are made that we should introduce this microscopic inspection into the United States. There are, however, numerous difficulties (legal, financial, practical, and theoretical) in the way of carrying out such a plan. It would cost, in the aggregate, several million dollars per year, and that sum of money could be spent to much better advantage in fighting tuberculosis or some other serious disease. The federal government could inspect the meat only at the registered abattoirs, and a system which has shown such poor results in Germany would certainly not appeal strongly to national, state, and

local legislative bodies when the heavy appropriation was demanded. To inspect the pork in sparsely settled portions of this country is an impracticable proposition. Further, experience has shown that the microscopic inspection gives a false sense of security, and even in Germany the authorities have repeatedly felt it necessary to warn the public not to trust to the inspection, but to protect against the disease by thoroughly cooking the pork. If pork is thoroughly cooked or thoroughly cured, there is no danger of contracting trichinosis; and since cooking and curing are methods which appeal to American and English tastes, we can well urge these upon hygienic grounds also. An extermination of rats would result in a decrease of trichinosis.

Pseudotrachinæ.—Various parasites have been mistaken for trichinæ. Thus a sarcosporidium (*Sarcocystis miescheriana*), which is exceedingly common in pork, has been repeatedly mistaken for trichinæ, but the fleshworm is usually wound in a spiral and enclosed in a much thicker cyst, while the *Sarcocystis* is more elongate, slender, straight, and with content that appears granular under the microscope; under high-power magnification, these granule-like bodies are seen to be more or less crescentic in form, somewhat similar to the crescents of estivo-autumnal malaria. The worms described as *Trichina affinis*, *T. agilissima*, *T. anguillae*, *T. cystica* (see p. 311), *T. cyprinorum*, *T. inflexa*, *T. lacertae* and *T. microscopica*, from various animals, are not trichinæ. Various strongyles also have been recorded as trichinæ. A very interesting case of pseudotrachinosis is presented in *Rhabditis terricola* (*R. cornwalli*, *Pelodera setigera*). This nematode was found in an exhumed cadaver of an English cadet, from the ship Cornwall and was mistaken for a trichina; on the basis of this erroneous zoölogical determination, the outbreak of disease which had occurred was pronounced trichinosis and attributed to American pork.

PULMONARY ROUNDWORMS

Metastrongylus apri (Gmelin, 1790) is a 12 to 50 mm. long thread-worm, which is rather common in the lungs of hogs. It has been reported by Diesing (1851*a*, 317) once for the lungs of man; Chatin (1888*b*) states that it also occurs in the stomach of man, but such cases are probably due to eating hogs' lungs containing the worms. Rainey's (1855) case of *Filaria trachealis* in the trachea and larynx of a human subject may possibly belong under *M. apri*. The eggs of *M. apri* measure 50 to 100 by 37 to 72 μ , and contain an embryo at oviposition.

SUBCUTANEOUS ROUNDWORMS

Gnathostoma siamense (Levinsen, 1889) is a very remarkable nematode which has been collected on two occasions from three similarly affected patients in Siam. It attains 9 mm. in length by 1 mm. in breadth; head globular, with 8 circles of simple spines; mouth with

two lips; anterior third of body with scale-like, tridentate spines, which become smaller and more simple the farther they are from the head. The brief description by Levinsen is based upon a female parasite collected from a Siamese in a superficial nodule on the side of the chest.

Rhabditis niellyi (Blanchard, 1885) is at present a nominal species which can scarcely be classified, even generically, with any degree of certainty. It is known only as a rhabditiform larva, 333μ long by 13μ broad, which was found by Nielly (1882*a*) in cutaneous papules, chiefly on the limbs, in a boy at Brest; small worms were also found for a time in the blood, but examination of the feces, urine, and sputum was negative. Authors have compared this case with craw-craw, and have explained the infection upon the assumption that the boy might have swallowed eggs in drinking water of poor quality; that the embryo then escaped and reached the blood and skin. Possibly an equally plausible explanation would be to assume a direct cutaneous infection after the manner of uncinariasis. Whittles (1903*a*) reports a case of hypertrophic gingivitis in a female, aged nineteen years, in whom small nematodes were found in the periosteum of the upper jaw after tooth extraction; the worms were also found elsewhere, as in abscesses in the skin.

Dracunculosis¹ or Guinea-worm Infection.—Geographical Distribution.—This is essentially an Old World infection, being endemic in India, Persia, Turkestan, Arabia, and certain parts of Africa. It was introduced into South America by the slaves, but does not appear to have flourished there to any great extent. Occasional imported cases are reported in other parts of the world, several being recorded for the United States (Francis, 1901*a*, and others).

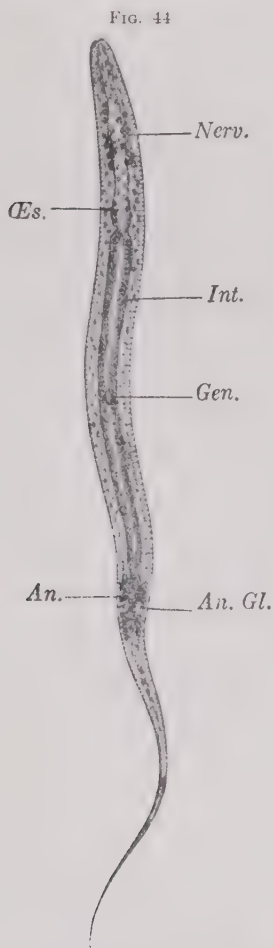
Zoölogical Distribution.—This parasite is reported not only for man but also for cattle, horses, dogs, and several wild animals. Manson has suggested that possibly some of these cases represent specifically distinct infections.

The Parasite.—The Guinea-worm or Medina-worm, *Dracunculus medinensis* (Linnaeus, 1758), is a white to yellowish parasite, 50 to 80 or more cm. long by 0.5 to 1.7 mm. in diameter; its anterior end is bluntly rounded, with a small terminal mouth and 6 papillæ. A vulva has not been discovered, the genital organs probably discharging through the œsophagus. The intestine is rather reduced and no anus is present in adult specimens. The uterus is enormously developed and filled with sharp-tailed embryos 0.5 to 0.75 mm. long by 0.17 mm. in maximum diameter.

Source of Infection.—The embryos escape, apparently through organs prolapsed through the mouth of the adult worm, and may live in clear water for six days, in muddy water or moist earth two to three weeks; if slowly dried, they resuscitate in water. They may enter small crustaceans (*Cyclops bicuspidatus*, etc.), and within about three weeks develop to 1 mm. in length, casting the skin two or three times, losing the long tail, acquiring a cylindrical shape, and developing a tripartite arrangement on the tip of the tail. They are then supposed to be swallowed in the drinking water. According to Plehn, a direct development without

¹ SYNONYMS.—Dracontiasis; Guinea-worm disease.

intermediate host is not excluded. It was formerly believed that the worm entered through the skin, and, as this mode of infection is now demonstrated for certain other worms, doubtless the possibility of this



Embryo of the Guinea-worm.
Nerv., nervous system; *Œs.*, oesophagus; *Int.*, intestine; *Gen.*, genital primordium; *An.*, anal papillae of glandular nature. $\times 199$.
 (Looss.)

method will again be considered in connection with this species. The further history, to the gravid condition, has not been followed, but probably the worms soon leave the intestinal canal and reach the connective tissue; after copulation the male probably dies, while the gravid female, about ten to fourteen months after infection, wanders to the subcutaneous tissue.

Symptoms.—The gravid parasite produces very painful, superficial, furuncle-like swellings, chiefly on the feet and legs (about 85 per cent. of the cases), and occasionally on other parts of the body, as the back, neck, head, wrist, scrotum, penis, etc. A small blister forms and elevates the epidermis; the blister ruptures, disclosing a superficial ulcer about three-fourths of an inch in diameter, at the centre of which there is a small opening about two millimeters in diameter, from which the head sometimes protrudes. There may be fever, chill, nausea, and vomiting. The swelling may last two or three weeks; then the worm is extruded and the wound heals; or premature death of the parasite may give rise to an abscess; or the worm may become calcified and be felt for years as a hard knot.

Treatment.—Emily's (1894a) treatment consists in injecting bichloride of mercury (1 to 1000) into the protruding worm, which can then be easily removed twenty-four hours later; or if the worm itself is not visible, a few drops of the solution are injected as near the coil as possible; the parasite may then be wound out or cut out. Another method is to protect the infected part from injury and douch it frequently with water; when this is done the uterus gradually empties and the

worm may be extracted or it may come out of its own accord. Traction should not be used so long as the parasite discharges embryos, a point which may be determined by microscopic examination of the fluid issuing from the opening. The old method of extraction is to pass a coil of the parasite through the cleft end of a small stick and to wind it out of the wound *very* slowly, making only one or two turns of the stick daily. The objection to this method is that the worm sometimes breaks, the embryos escape into the surrounding tissue; violent inflammation ensues, with

fever, abscess, and sloughing, and weeks or months may elapse before the patient recovers; death may occur from septic infection. Cummings (1910) prefers gradual traction to the perchloride method.

Prevention.—Upon the theory that the infection takes place through the drinking water, only filtered or sterilized water, or water of unquestionable origin should be taken when in an infected region.

FILARIASIS

Infections with Threadworms of the Genus *Filaria*.¹—The genus *Filaria* Müller, 1787, includes long, slender, filiform threadworms with curved or spiral tail. The male is smaller than the female, has 2 unequal spicules, 4 preanal papillæ, and a varying number of postanal papillæ; in the females the vulva is near the anterior end. The adults are parasitic, especially in the connective tissue, lymphatics, and body cavities; the embryo or larva frequently inhabits the blood, and in several species for which the life-history is known, insects such as mosquitoes form the intermediate host. Recently the genus *Filaria* has been divided into a number of distinct genera, so that a change of technical names is unavoidable.

Quite a number of species are reported as parasitic in man, but not all of them are described with sufficient accuracy to permit a positive zoölogical determination. In medical literature the chief interest has centred around the so-called *Filaria sanguinis hominis*. As a matter of fact, the name *Filaria sanguinis hominis*, as used in literature, means but little more to zoölogists than does the expression "the tadpoles of Virginia." In recent years *Filaria sanguinis hominis* is becoming confined more and more to one species, namely, to *Filaria bancrofti*; but as a scientific name it should be eliminated from medical literature. The various young filariæ described for the blood of man are sometimes referred to under the generic name *Microfilaria*, which from a standpoint of nomenclature is simply the name of a collective group of Filariidæ in an immature stage; the microfilaria of man may be tabulated as follows:

KEY TO THE FILARIA LARVÆ FOUND IN HUMAN BLOOD

Sheath present:

Periodicity absent; sheath very close; tail constricted, then sharply pointed; body 292 to 330 by 65μ ; type locality, Manila, P. I.; *F. philippinensis*, p. 315.

Periodicity present:

Nocturnal periodicity (?); tail truncated; body 131 by 5.3μ ; type locality, Bombay; *F. powelli*, p. 315.

Nocturnal periodicity:

Tail sharply pointed; body 317 by 7.5μ ; type locality, Australia; (*F. nocturna*) *F. bancrofti*, p. 306.

Tail truncated; body 164 by 8μ ; type locality, Japan; *F. taniguchii*, p. 313.

Diurnal periodicity:

Body 317 by 7μ ; type locality, West Africa; (*F. diurna*) *F. loa*; p. 312.

Sheath absent; no periodicity:

Tail sharply pointed; Body 210 by 5μ ; type locality, West Indies; *F. demarquayi*, p. 314.

Body 215 by 5μ ; type locality, British Guiana; *F. ozzardi*, p. 313.

Tail blunt, truncated: Body 195 by 4.5μ ; type locality, West Africa; *F. perstans*, p. 313. Body 220 to 240 by 8 to 12μ ; type locality, West Africa; *F. gigas*, p. 315.

¹ For the most recent zoölogical summary of the species reported for man, see Penel (1905, *Les filaires du sang de l'homme*, Paris) and Stiles, 1907b (*Bull. No. 34*, Hygienic Laboratory).

So far as can be discovered, none of these young worms does any appreciable injury in the blood, and of the adult worms only one, namely, *Filaria bancrofti*, can at present be viewed as serious; while a second species, *F. loa*, is more or less troublesome. We are hardly justified at present in assuming that all the other species are entirely without effect upon their hosts, but just what their effect is has not been shown, and whatever it may be, the indications are that at least in cases of light infection, that effect is of secondary importance when compared with *F. bancrofti*.

ADULT WORM.	LARVA ¹ KNOWN AS—	TYPE LOCALITY AND GENERAL DISTRIBUTION.
<i>Filaria bancrofti</i> Cobbold	<i>F.</i> or <i>M. nocturna</i> Manson	Australia; tropics
<i>F. (Loa) loa</i> (Cobbold)	<i>F.</i> or <i>M. diurna</i> Manson	West Africa; India.
<i>F. perstans</i> Manson	<i>F.</i> or <i>M. perstans</i> Manson	West Africa.
<i>F. ozzardi</i> Manson	<i>F.</i> or <i>M. ozzardi</i> Manson	British Guiana.
<i>F. demarquayi</i> Manson	<i>F.</i> or <i>M. demarquayi</i> Manson	West Indies.
<i>F. [Onchocerca] volvulus</i> Leuckart		Gold Coast; West Africa.
<i>F. taniguchii</i> Penel	<i>F.</i> or <i>M. taniguchii</i>	Japan.
<i>F. [Setaria] equina</i> (Abildgaard)		Europe; rather cosmopolitan.
<i>F. [Dirofilaria] immitis</i> Leidy		Pennsylvania; probably cosmopolitan.
<i>F. [D.] magalhães</i> Blanchard		Rio de Janeiro.
<i>F. lentis</i> Diesing		Europe.
<i>F. conjunctivae</i> Addario		Italy; Hungary.
<i>F. juncea</i>		
<i>F. labialis</i> Pane		Italy.
<i>F. kilimarae</i> Kolb		Kilimara, East Africa.
<i>F. romanorum orientalis</i> Sarcani		Roumania.
(Unknown)	<i>F. gigas</i> Prout	Sierra Leone; West Africa.
(Unknown)	<i>F.</i> or <i>M. powelli</i> Penel	Bombay.
(Unknown)	<i>F.</i> or <i>M. philippinensis</i> Ashburn and Craig	Manila, P. I.

Infection with *Filaria Bancrofti*.—Geographical Distribution.—Australia is the type locality for this parasite, but it may be designated in general terms as a tropical and subtropical infection of Asia, Africa, and America. It is especially common on the west coast of Africa, in South China, certain parts of India, Samoa, Friendly Islands, West Indies, etc. In the United States cases are occasionally found in the Southern States; Mobile (Anderson); Charleston, S. C. (Guiteras and others); occasional cases are found farther north.

Zoölogical Distribution.—The adult worm is thus far known only for man. The larva occurs in a number of mosquitoes (*Anopheles*, *Culex*, and *Panoplites*).

¹ The custom of giving to the larva a special specific name is not favored by the International Code of Zoölogical nomenclature. Were we to give the egg of a mosquito one name, its larva a second, its pupa a third, and the adult a fourth, no end of confusion would result. A species is entitled to only one valid name.

The Parasite.—Bancroft's filaria¹ (*Filaria bancrofti* Cobbold, 1877) is a whitish or brownish, (?) transversely striated worm, 44 to 95 mm. long by 0.1 to 0.26 mm. in diameter; male with two spicules, 0.2 and 0.6 mm. long, anogenital pore 138μ from tail, preanal papillæ uncertain, but apparently 3 pairs of postanal papillæ; vulva of the female 0.66 to 0.75 (or 1.2 to 1.3 mm.) from head, anus 225μ from tip of tail. Viviparous. The larvæ, 300 to 340μ long by 6.6 to 8.5 or 11μ in diameter, are found in the circulating blood and are provided with a sheath and sharply pointed tail; they show a more or less marked periodicity in that they are much more numerous in the peripheral circulation during the night; but if sleep is reversed to daytime, the periodicity also is reversed. Mosquitoes, while biting patients, swallow these larvæ, which then undergo development in the muscles, and finally, after fourteen to seventeen days, or, by lower temperature, up to thirty-five or forty-one days from time of infection, the worms reach a stage in which they are transmitted to man during the bite of the mosquito.

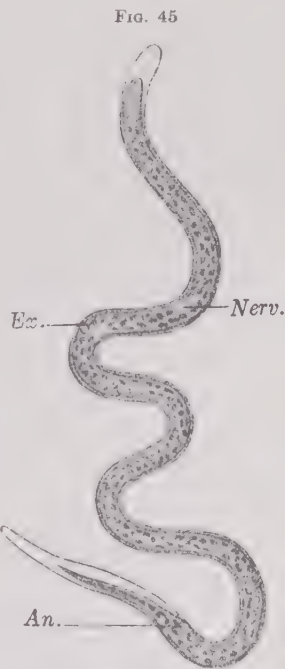
Nothing is known of the biology of the worm from the time it enters man up to the adult stage. The adult worms occur alone or as several coiled together, chiefly in the lymphatics, but also occasionally in the fluids in swollen organs. There is no satisfactory explanation, as yet, of the periodicity shown by the larva.

Source of Infection.—The mosquito.

Frequency.—This varies with exposure to infected mosquitoes. In some places the infection is rare; in others it increases to 5, 10, 20, 50, or more per cent. of the inhabitants.

Duration.—Nothing positive is known regarding the longevity of the adult or larva, but apparently neither is very short-lived.

Symptoms.—That numerous cases of infection show no appreciable symptoms is well established, but that in other cases the worms produce serious results must be admitted, especially if the adult parasites are present in large numbers or unfortunately located. According to Manson, *Filaria bancrofti* may produce the following conditions: abscess, lymphangitis, varicose groin-glands, varicose axillary glands, lymph scrotum, cutaneous and deep lymphatic varix, orchitis, chyluria, elephantiasis of the leg, scrotum, vulva, arm, mamma, etc.,



Larva of *Filaria bancrofti* in the blood of man in Egypt. Nerv., nervous system; Ex., excretory; An., anus. $\times 514$. (Looss.)

¹ SYNONYMS.—*Filaria sanguinis hominis* Lancet, London, August 31, 1872, p. 310; larva; type locality, Calcutta (Lewis). *F. dermatemica* da Silva Araujo (1875); type locality, Bahia. *F. bancrofti* Cobbold, July 14, 1877; adult; type locality, Australia. *F. wuchereria* Magalhães, 1877, and *F. wuchereria* da Silva Lima, 1877; type locality, Brazil. *Wuchereria filaria* Silva Araujo, 1877. *F. nocturna* Manson, 1891; larva.

chylous dropsy of the tunica vaginalis, chylous ascites, and chylous diarrhœa. In not all of these cases is the exact method by which the parasites act fully understood, and the relation of the parasites to elephantiasis is based chiefly upon circumstantial evidence. In general, the adult parasites, or, Manson believes, in some cases, "their immature products of conception," cause two principal types of filariasis, one characterized by a varicosity of the lymphatics, the other by a more or less solid œdema.

The frequency of these various manifestations does not seem to be uniform in filarial patients in different geographical areas, but the reason for this variation is not at present clear.¹

Filarial Abscess.—These may be present in various affected organs and may contain the dead adult worms. They may discharge or be opened; if in the thorax or abdomen they may be serious. According to Manson, deep-seated pain in the thorax or abdomen, with inflammatory processes followed by hectic fever and a diminution in the number of or disappearance of filaria larvæ in the peripheral blood, suggest filarial abscess and indicate exploration, and, if feasible, operation.

Lymphangitis.—Elephantoid Fever.—This is common in all forms of filariasis due to *F. bancrofti*; it may or may not be followed by more severe conditions, as elephantiasis, lymph scrotum, varicose glands, etc. It usually appears on the extremities, but may be confined to other parts of the body (groin-glands, testis, spermatic cord, or abdominal lymphatics). The attack continues for several (usually two) days, then may recur after weeks, months, or years. It begins with a severe and prolonged chill (rigor), followed by high fever, 105.8° F.; is accompanied by headache, loss of appetite, frequent vomiting, and even delirium; it ends with profuse perspiration. At the onset of lymphangitis of the extremities, the painful cord-like swelling of the lymphatic trunks and of their glands, with a red, congested streak in the overlying skin, is visible; abscess or gangrene may develop; finally the tension is relieved by lymphous discharge and the swelling partially subsides, but the skin and subcutaneous tissue do not return to quite their normal condition, some permanent thickening remaining. Elephantoid fever has been repeatedly mistaken for malaria, but a differential diagnosis should not be difficult; in some localities it is erroneously called "fever and ague." The filaria embryos are not always found in the blood. In *treatment* elevate the affected part, compelling absolute rest; give a milk diet; use mild laxatives, cooling lotions or warm fomentations, opium to relieve pain, and scarify the swollen area if necessary to relieve tension.

Varicose Groin-glands, Helminthoma Elasticum.—These frequently accompany lymph scrotum but may occur with other filarial manifestations; the affection may be unilateral or bilateral. They are soft, doughy, obscurely lobulate, and stationary in position; but the skin may be readily moved over them. They may be easily mistaken for

¹ Is it possible that local conditions, incident to the geographical distribution, have resulted in differentiating *F. bancrofti* into several subspecies, each with special tendency to a given clinical manifestation? Or have we in man even a larger number of distinct species of *Filaria* than have yet been described?

hernia. If the patient lies with raised pelvis the swelling slowly disappears; but if he stands erect the swelling slowly returns while the hand is pressing against the saphenous or inguinal openings. The contents are white to red, chylous, rapidly coagulable fluid, and usually contain filaria larvæ. This condition is frequently mistaken for hernia, but the swellings are not tympanitic on percussion; upon pressure they disappear slowly, and there is no gurgling; there is little or no impulse on coughing. Manson emphasizes the fact that chronic swellings about the groin, cords, testes, and scrotum in patients from the tropics should always be regarded as of possible filarial origin. They are best left alone unless they result in an incapacitating discomfort, when they may be removed. Operation is not however, always satisfactory, as it may be followed by lymphorrhagia, excessive dilatation of some other part of the lymphatic area, chyluria, or by elephantiasis. Upon Manson's advice, Godlee, in order to prevent lymph stasis, drained the lymphatics of the region operated on into the vena spermatica and v. saphena, obtaining good results.

Superficial or Deep Lymph Varices.—These are not rare, and may be superficial on the abdomen, legs, or other parts of body; or they may be more deeply located. If they rupture, lymphorrhagia results. They may appear and disappear within a few hours, and indicate lymphatic obstruction.

Lymph Scrotum.—This is frequently accompanied by varicose groin and femoral glands. The skin is silky to the touch, but presents lymphatic varices which may open and discharge milky to bloody, rapidly coagulating lymph, usually containing filarial larvæ, which are also present in the blood. Elephantoid fever probably results from external mechanical irritation; the scrotum may become thickened, and elephantiasis may develop. In treatment, support and protect the scrotum, which should be kept clean and powdered; but otherwise leave it alone unless inflammation be frequent, debilitating lymphorrhagia be present, or elephantiasis develops. If operation is decided upon, excise all the diseased tissue, obtaining flaps from the thigh if necessary. The patient should be warned of the possible occurrence of chyluria or of elephantiasis of the leg as a result of this surgical interference.

Chyluria; Hematochyluria.—This is very common, but intermittent; it may appear without warning or may be preceded by pains in the back, pelvis, and groin; the first symptoms may be retention of urine due to chylous coagulation in the bladder; the color of the discharge varies from a milky-white to a blood tinge, not only in different cases but also in the same case. It is rarely continuous; attacks occur usually lasting weeks or months or up to two years (Sheube), with more or less prolonged intervals. While not directly dangerous, the continued drain upon the system may result in anemia, debility, depression, and incapacity for active life. Attacks are favored by pregnancy, childbirth, running, and other violent exertions which lead to rupture of a lymphatic varix in the bladder wall.

Treatment consists in absolute rest in bed, with elevated pelvis, a light saline purge, vesical irrigation, and restriction of food (especially

fats) and fluids. Various drugs (gallic acid, benzoic acid, salol, chromic acid, glycerin, tincture of perchloride of iron, methylene blue, quinine, ichthyol, etc.) have gained some reputation, but Manson is of the opinion that they have no effect whatever. Filarial larvæ may be numerous in the urine.

Orchitis.—This occurs as an acute manifestation accompanied by headache and vomiting, and disappears as rapidly as it appears. It is preceded by elephantoid fever; there is a very rapid and very painful inflammation of the testes, which are much swollen; the swelling may also involve the epididymis, spermatic cord, and entire scrotum. Afterward, the fluid in the tunica vaginalis may not be entirely absorbed but may lead to chylocele. Filariae are often present in the blood. Manson suggests the possibility that the "malarial orchitis" of certain authors may in reality be a filarial orchitis.

Chylocele.—This manifestation is more or less common, either alone or more frequently with or as a result of varicose lymph glands, lymph scrotum, etc. In the morning it is always soft and it is never so tense as common hydrocele. Numerous filarial larvæ are present in the milky, reddish, quickly coagulating content. Treatment is identical with that of ordinary hydrocele.

Elephantiasis.—The recurring attacks of elephantoid or erysipelatoid fever, with resulting and accumulative thickening of the affected part, gradually give rise to an elephantiasis, which, according to Manson, is the most frequent manifestation of this filarial infection. Occasionally, however, progressive elephantiasis may occur after only one or several attacks of elephantoid fever. It is estimated that in 95 per cent. of the cases, the elephantiasis occurs in the legs, either alone or with elephantiasis of the scrotum or arms. Elephantiasis of the scrotum is also common, while that of the arms, mammae, vulva, and limited areas of the skin (pedunculated elephantoid tumors) is more rare. In only a proportion of the cases are the filariae found in the blood or in the fluid of the diseased organ.

The skin is rough and coarse, the hair is coarse and sparse, and the nails thick and deformed. The part pits but slightly or not at all on pressure, and does not glide over the underlying tissues. The skin is dense, fibrous, and enormously hypertrophied; the connective tissue is hypertrophied and "blubbery" from its infiltration with lymph; bloodvessels are large; the lymphatics are dilated and the lymphatic glands enlarged. As even slight injury to the affected part may induce a recurrence of the elephantoid attacks, care must be taken to protect it. Violent exercise, exposure to the hot sun, etc., should be avoided. Massage, elevation of the affected part to drain out the lymph, and elastic bandaging, are to be encouraged. Absolute rest in the recurrent attacks of fever should be insisted upon; unfortunately permanent recovery never occurs.

In extreme cases of *elephantiasis of the leg*, good results are sometimes obtained by excising a longitudinal strip 3 to 4 inches in breadth by 12 or more inches in length; during the febrile attacks, tension may be relieved by punctures with a lancet under aseptic conditions.

Elephantiasis of the scrotum frequently develops to tumors of 10, 15, 20, 40, or 50 pounds; Manson gives 224 pounds as the largest case on record. These enormous growths are unsightly and inconvenient, but not, as a rule, directly dangerous. Occasionally they endanger life by becoming gangrenous or by abscess formation. They may develop either rapidly, in two or three years, or very slowly. Upon reaching such a size that they are unsightly or inconvenient, surgical interference is indicated. The reader must be referred to works on surgery or to special papers on this subject for the full technique of operation.

For *elephantiasis* of the arm, massage and elastic bandaging are used.

A number of authors doubt whether elephantiasis is due to *Filaria bancrofti*. The general weight of circumstantial evidence seems, however, to indicate that at least some cases are due to this cause, while other cases which might formerly have been attributed to this worm may perhaps be due to other causes—as streptococcus infection. Brault recognizes a bacterial (streptococcus) and a filarial elephantiasis.

Diagnosis.—An attempt should always be made to find the larval filaria in the blood, urine, or chylous accumulation. There are chances for error in connection with the examination of the urine, and probably all those cases in which eggs are reported for the urine should be definitely rejected. *Trichina cystica* Salisbury, for instance, which nearly all authors have identified with *Filaria bancrofti*, is doubtless *Oxyuris vermicularis*; vinegar eels (*Anguillula aceti*) have also been mistaken for filariæ. **Blood:** The lymphocytes increase to 24 to 40 per cent.; the eosinophiles to 8 to 18 per cent.

Prognosis.—While filariasis is generally admitted to be a disease which cannot be absolutely cured, the prognosis in uncomplicated cases is reported as good. Even in severe infections life may not be in danger.

Treatment.—Treatment to exterminate the larvæ in the blood is not only rather unsuccessful but also unnecessary. Authors have claimed, however, that they may be reduced in numbers with thymol, ichthyol, etc. The writer takes exception to the view that such treatment is undesirable, if found to be practicable, as such eradication of the larvæ would naturally be an important point gained in prevention. Anthelmintic treatment, directed against the adult, is in our present knowledge not only useless, but apparently undesirable, as the dead worm is viewed as more dangerous than the live parasite.

With Manson, the symptomatic treatment is generally admitted as consisting in rest, lowering the tension of the lymphatics by saline purgatives, by appropriate food, and limitation of fluids ingested. Several drugs (potassium iodide, gallic acid, methylene blue, ichthyol, etc.) have gained a temporary reputation, but the conclusion drawn is that their administration accidentally coincided with the time of spontaneous remission. The necessity for asepsis in operation is so self-evident that it need not be emphasized here. Manson advises postponement of operation so long as convenient, but some authors are less conservative on this point.

Prevention.—Every person who shows the filaria larvæ in the blood, independently of the fact whether any pronounced symptoms are

present, should, because of the danger of spreading the infection by mosquitoes, be considered a danger both to himself and to the persons in his neighborhood. This danger can be checked by compelling him to sleep under a mosquito-bar.

Infection with the Loa.—**Geographical Distribution.**—This infection is known particularly for the west coast of Africa, but imported cases are reported for other localities, chiefly in slaves or in missionaries who have visited Western Africa. Ward (1906) collected the recorded cases and published several new cases for North America.

Zoölogical Distribution.—The loa is positively known only for man, but Blanchard states that according to Plehn (1898) the natives say it also occurs in sheep and goats.

The Parasite.—*Filaria (Loa) loa*¹ (Cobbold, 1864) is a filiform, colorless to yellowish-white threadworm, 16 to 57 mm. long by 0.3 to 0.57 mm. in diameter; the cuticle is not striated but is provided with numerous wart-like structures, not known for any other *Filaria* found in man; male with lateral caudal alæ; 3 pairs of preanal pedunculated papillæ, decreasing in size from the anterior to the posterior, and two or possibly three pairs of smaller postanal papillæ; spicules unequal, 113 and 176 μ long; vulva of female 2.35 to 2.4 mm. from head; viviparous. The larva (*F. diurna*) circulates in the peripheral blood during the day. Life-history unknown.

Manson's view that *F. diurna* represents the larva of *F. loa* is not accepted by all authors, and in fact he, himself, merely suggested it as a possibility. The point raised by several authors, that not all loa patients show *F. diurna* in the blood examinations, is not a very strong argument against the hypothesis, for it is perfectly possible that they were not examined at a time when the parasites were laying their young. In September, 1904, through the kindness of Sir Patrick Manson, the writer saw in London a lady who had been in West Africa and had just come to him to have a loa extracted; she also had *F. diurna* and gave a history of Calabar swelling. Other observations seem to raise Manson's hypothesis practically to a certainty.

Source of Infection.—This is not yet determined. There is a popular impression that infection occurs through the drinking-water, but analogy would point to some insect as intermediate host. Manson suspects that mangrove flies (*Chrysops dimidiatus*) play this rôle; experiments on certain mosquitoes (*Anopheles costalis* and *A. funestus*) have been negative, but positive on *C. dimidiatus* and *C. silacea*.

Duration.—*Filaria loa* is apparently rather long-lived; it has been seen in persons who had been away from the infectious locality for from four to ten or eleven years.

Symptoms.—This parasite inhabits the connective tissue all over the body, which it traverses freely; recent observations indicate that it is quite superficial; it is seen especially around the eye in the subcutaneous

¹ SYNONYMS.—*F. oculi* Gervais and van Beneden, 1859; *Dracunculus oculi* (Gervais and van Beneden, 1859) Diesing, 1860; *D. loa* Cobbold, 1864; *F. subconjunctivalis* Guyon, 1864; *F. diurna* Manson, 1891; *F. sanguinis hominis major* Manson, 1891. *F. sanguinis diurna* Fagge and Pye Smith, 1902; *F. bourgii* Brumpt.

fascia about the orbit, between the conjunctivæ and bulbus; it travels over the nose, in the fingers, penis, etc. It disappears from the surface in two or three days and reappears after some days, weeks, or months. Its appearance is favored by warmth and retarded by cold.

The loa causes an itching, creeping, prickling sensation, with occasional cedematous swellings and in some cases lachrimation or considerable pain; it may determine a more or less intense conjunctivitis and disturbances in vision. Several authors have associated with loa infections the so-called "Calabar swellings" and "Kamarunbeulen;" these appear suddenly on various parts of the body as elevations about half the size of a goose-egg, or 40 to 60 mm. in diameter; they wander slowly, about 20 to 30 mm. per day, then disappear in about three days to reappear after some months or years; they are painless, but slightly irritating; do not pit on pressure, and feel "somewhat hot both objectively and subjectively;" they may occur on any part of the body, but, according to one patient, are caused by rubbing or scratching to relieve the irritation produced by the worm.

Treatment.—When the loa approaches the surface it can readily be seen beneath thin skin; for instance, in the eyelid or over the bridge of the nose. It is then secured by means of forceps, an incision is made, and a second pair of forceps used directly on the worm; the first pair of forceps is then released and the worm drawn out with the second pair. Manson relates that the natives extract the parasite by means of a sharp thorn, or drive it into the deeper tissue by dropping a grain of salt into the conjunctival sac. He suggests the injection of bichloride of mercury (1 to 1000) when the worm appears in parts of the body other than near the eye.

Filaria taniguchii Penel, 1905, is reported as 68 mm. long (female), 0.2 mm. in maximum diameter; the vulva is 1.3 mm. from the anterior extremity, the anus 0.23 mm. from caudal end; cuticle unstriated; anterior end with 2 pairs of buccal papillæ; eggs 40 by 25 μ ; embryos in utero measure 290 μ long by 7 μ in diameter. The adult is found in the lymphatic ganglia. Male unknown. The larvæ show a nocturnal periodicity in the peripheral blood; they measure 164 μ long by 8 μ in diameter; a sheath is present, the tail is truncated. Type locality, Ama Kusha, Japan.

Filaria perstans Manson, 1891, was based upon filarial larvæ (see p. 306) found in West Africa in the peripheral circulation both night and day. Adult worms, 45 to 80 mm. long, have now been found in the fat connective tissue in upper part of the mesentery and elsewhere, which are assumed to be its adult stage. The male is said to have 4 pairs of preanal and 1 pair of postanal papillæ; in the female, the vulva is 0.6 mm. from the mouth, the anus 0.145 mm. from the tail. The head in both sexes is large and the tail is described as having 2 minute triangular projecting appendages, giving it a mitered appearance. This parasite is also reported for British Guiana. This species has been reported in the chimpanzee also.

Filaria ozzardi Manson, 1897, is reported for connective tissue in British Guiana; the worms are 38 to 81 mm. long; male without (?) any

caudal papillæ; in female, vulva 0.71 mm. from mouth, anus 0.23 mm. from tail. Larvæ (see p. 306) in peripheral blood night and day. This species is not thoroughly established.

Filaria demarquayi Manson, 1895, is a threadworm which has been reported for St. Vincent, West Indies (type locality), St. Lucia, Dominica, and Trinidad. The male is not known. The female measures 65 to 80 mm. long by 0.210 to 0.250 mm. in diameter; the vulva is 0.76 mm. from the mouth; anus 0.25 mm. from the tail; it lives in the subperitoneal connective tissue and is known only for man. The embryo lives in the blood, is 200 to 210 μ long by 5 μ in diameter, without sheath; the tail is sharply pointed; movements are very active; they do not exhibit any daily periodicity. The life-history is unknown and experiments on mosquitoes have thus far been negative. Wellmann believes that a tick (*Ornithodoros moubata*) is the intermediate host.

Filaria [or] **Onchocerca volvulus** Leuckart, 1893, has been reported in subcutaneous tumors, in patients from West Africa. The male measures 30 to 35 cm. long, and has two unequal spicules (Prout), 82 and 177 μ long; tail strongly incurved. The female measures 60 to 70 μ , and is viviparous. The embryos are 250 μ by 5 to 6 μ , without sheath, and with sharp tail. These have been found in tumors, but not in the blood. According to Labadie Lagrave (1899) the worm is in a lymphatic canal.

Filaria [or **Dirofilaria**] **magalhãesi** Blanchard, 1895, has been found but once, in the left heart of a child in Rio de Janeiro. The male is 83 mm. long, with 4 preanal and 4 postanal peculiar papillæ with scalloped outline; shorter spicule 0.23 mm. long, longer spicule not measured; female 155 mm. long; vulva 2.56 mm. from head; cuticle with transverse striation. Nothing is known regarding the life-history or medical importance of this worm.

Filaria [or **Dirofilaria**] **immitis** Leidy, 1856, is a 12-to-30-cm. long threadworm found in the right half of the heart of dogs. Mosquitoes (*Anopheles* and *Culex*) form the intermediate host. Bowlby is said to have reported its presence in the portal vein of man, but the zoölogical determination is open to question. It has been claimed that the worm in question was undoubtedly a blood fluke (*Schistosoma haematobium*).

Filaria conjunctivæ Addario, 1885, is a filiform, 5.5 to 16 cm. long, white to brownish nematode which occurs in the eye, ligamentum gastro-lineale and in cysts on the forearm of man, and in the eye of horses and asses, in Europe (Italy, Hungary). Five cases are reported for man. Only the female parasite has been seen and nothing is known of the life-cycle.

(? **Filaria**) **labialis** Pane, 1864, has been reported but once, from the upper lip, in Naples. It measures about 30 mm. long; mouth with 4 papillæ; vulva 2.5 mm. from anus; anus 0.5 mm. from tip of tail.

Agamofilaria oculi (*F. lentis* Diesing, 1851) is a *species inquirenda*; worms varying from 1.72 to 12.6 mm. in length have been classified here; they were found in 3 cases of cataract. Errors in interpretation of supposed filariæ in the eye are likely to occur, and remnants of the hyaloid artery may be mistaken for nematodes unless a microscopic examination of

the structure is made. Braun excludes the cases reported by Quadri (1857), Fano (1886a), Schoeler (1875), and Eversbusch (1891), but accepts those of Nordmann (1832), Gescheidt (1833 *a*, p. 405), and Kuhnt (1891).

Agamofilaria georgiana Stiles, 1907, is an immature worm of uncertain systematic position, found in a superficial sore on the ankle of a negress in Georgia. It measures 32 to 53 mm. long by 560 to 640 μ in maximum diameter and its mouth is surrounded with 2 small lateral papillae and 4 large submedian lip-like papillae.

Filaria [Setaria or Hamularia] equina (Abildgaard, 1789) is a more or less common parasite in the abdominal cavity, occasionally in the pleural cavity, liver, skull, and elsewhere, of horses and asses; and several cases of its accidental presence in man have been reported. (Pleural cavity, Linstow, 1902; bronchial glands, Treutler, 1793; Brera, 1811; Blanchard, 1890 *a*, 16.) The parasite measures 6 to 22 mm. long, and has a very characteristic blunt cephalic end, provided with two lateral semilunar lips. Its life-history is not known.

Filaria juncea is reported for the connective tissue at the root of the mesentery.

(? **Filaria**) **kilimarae** Kolb, 1898, is at present a nominal species (type locality Kilimara, British East Africa). It attains 10 to 20 cm. in length by 0.5 to 1 mm. in diameter; is white in color, and resembles *Gordius aquaticus* in general appearance, while the oral papillae are very similar to those of *Dracunculus medinensis*. Man is the type-host, and the worms are said to occur in the abdominal cavity, vomit, and stools.

(? **Filaria** or ? **Microfilaria**) **romanorum orientalis** Sarcani, 1888, is said to be an adult threadworm 1 mm. long, found in Roumania.

Filaria [Microfilaria] powelli Penel, 1905, is a small larval filaria reported for the blood in Bombay; it measures 131 μ long, 5.3 μ in diameter, is provided with a sheath, and has a slender truncated tail; periodicity "nocturnal?"; the adult is unknown.

Filaria [Microfilaria] philippinensis Ashburn and Craig, 1906, a larval filaria found in the blood of man in the Philippines (see p. 305). Its medical importance is not yet known.

(? **Filaria**) **gigas** Prout, 1902, is based upon two embryonic filaria structures, 220 to 340 μ long by 8 to 12 μ broad, found in the blood of a native at Moyamba, Sierra Leone. The head is rounded, tail tapers but ends bluntly, no sheath could be seen, and the animal stained readily with fuchsin. Looss (1905, p. 170) suggests the possibility that these represent empty sheaths—namely, cast skins; Low (1905) considers that this supposed species was based upon a contamination, probably with insect hairs.

NEMATODES OF THE UROGENITAL SYSTEM

Anguillula aceti (Müller, 1783), the vinegar-eel, has been reported several times¹ for the human bladder. It is a very small worm, 1 to 2

¹ See Stiles and Frankland, 1902 *a*, pp. 35 to 40, Figs. 7 to 13; and Billings and Miller, 1902 *a*.

mm. long by 24 to 40 μ broad; male with two equal spicules, 38 μ long, and accessory piece; vulva near equator; embryos 222 μ long by 12 μ in diameter. The mode of infection has not been demonstrated, but in at least one case it was possibly by means of vaginal douches acidulated with vinegar. No symptoms traceable to the parasite were noticed. The chief importance in connection with this parasite is the possibility of mistaking it for *Filaria*.

Leptodera pellio (Schneider, 1866) is recorded (as *Rhabditis genitalis* Scheiber, 1880) as a chance parasite of the vagina and thence in the urine in a case in Hungary reported by Scheiber (1880). The worms measure 0.8 to 1.3 mm. in length; caudal bursa of male with 7 to 10 rays each side; spicules 27 to 33 μ ; vulva slightly posterior of equator; eggs 60 by 35 μ . Infection may have taken place by means of poultices made of moist earth. (Compare *Anguillula mucronata* Grube, 1849, of earthworms.) Rhabditiform worms are also reported for the urine by Baginsky (1887*b*) and Peiper and Westphal (1888). Upon several occasions the writer has found rhabditiform embryos in the urine which he has been unable to identify zoologically.

Diectophyme renale¹ (Goeze, 1782), the giant strongyle, or canine kidney-worm, measures 40 cm. (male) to 100 cm. (female) long, and is red in color. It is found in the kidneys of dogs and various other animals, and about a dozen authentic cases have been recorded for man. Most of the cases reported for man involve erroneous zoological determinations; as eelworms, clots, etc., are mistaken for the giant strongyle. Diagnosis is made by finding the characteristic eggs, 64 to 40 μ , with peculiar mosaic-like shell, in the urine. Treatment is surgical. The source of infection is not determined.

Agamomermis restiformis (Leidy, 1880) is a vivid-red worm, 26 inches long, 1.5 mm. in diameter, which is supposed to have been passed *per urethram* by man in West Virginia. Only one case has been reported. This worm was originally reported as a *Filaria* but reëxamination of the original specimen by the writer has shown that this is an *Agamomermis*.

LEECHES, ACARIASIS, TONGUE WORM INFECTIONS, MYRIAPODA, PARASITIC INSECTS²

INFECTION WITH LEECHES (HIRUDINEI)

The blood-suckers resemble earthworms much more closely than they do the intestinal worms. They have a mouth at one end and a sucker at the other. The ordinary medicinal leech belongs to this group. Several species are troublesome to man, more especially in the tropics.

Limnatis nilotica (Savigny, 1820) occurs in North Africa; it is occasionally taken into the mouth with drinking-water, and it fastens in the nose, pharynx, œsophagus, or larynx. It has also been found in

¹ SYNONYM.—*Eustrongylus gigas* (Rudolphi, 1802) Diesing.

² For literature, apply to United States Bureau of Entomology.

the vagina and on the conjunctiva. When found, it should be secured with a pair of tweezers, then injected with salt water by means of a hypodermic syringe, and removed as it loosens its hold.

Some blood-suckers, such as the Mexican *Haementeria officinalis*, occasionally cause symptoms of poisoning, when used to draw blood. Other leeches in certain tropical localities are said to cause considerable irritation by fastening to the body as persons walk through the grass or brush.

ACARIASIS—INFECTION WITH ACARINES

The acarines include the mites and ticks; they have a segmented or an unsegmented body with 8 legs in the adult stage and 6 legs in the larval stage. Quite a large number of these animals attack man and animals, in some cases acting as the direct cause of disease, in other cases as the transmitter of other parasites.

Treatment.—The general rule applies that in all treatment sulphur should be used in some form, as sulphur ointment, etc., as this is particularly obnoxious to this group of parasites.

Ixodiasis—Tick Infection.—The ticks (Ixodoidea)¹ are divided into two families: the *Argasidae*, in which the capitulum ("head") is subterminal in the adults, and the *Ixodidae*, in which the head is terminal in adults. Quite a number of different species are known to attack man. In the United States the two species which have attracted the most attention within recent years are *Boophilus annulatus* (the intermediate host of Texas fever) and *Dermacentor andersoni*. Wilson and Chowning suggested that this tick acts as the carrier of Rocky Mountain "spotted fever"), and King (1906) and Ricketts (1906) have demonstrated the correctness of this view.

The Persian Argas (*Argas persicus*) enjoys the reputation in North Persia of causing a disease accompanied by extreme lassitude, fever, perspiration, severe pain, delirium, convulsions, and sometimes death. *Argas reflexus*, the pigeon-tick, attacks man, as an ectoparasite, causing a general erythema and a rapidly developing edema. *Argas miniatus* is also known to attack man. The spinose ear-tick (*Ornithodoros megnini*) is an American species which enters the ears of cattle, deer, dogs, and swine, and occasionally of man, causing considerable suffering. It can best be removed by pouring some bland oil into the ear.

South African tick-fever is an African disease which is transmitted by ticks belonging to the species *Ornithodoros savignyi*, and is accompanied about five to ten days after the tick-bite (which causes a small swelling) by a sensation of pain and itching followed by vomiting and purging, fever and rigors, often delirium; the attack lasts about two days to a week, or fever may continue three or four weeks. This should not be confused with Anderson's tick-fever (Rocky Mountain "spotted fever").

O. turicata and *O. talaje* are reported as ectoparasites of man in Central America and *O. tholozani* in Persia.

¹ For the North American species see Salmon and Stiles, 1901 a.

Dermacentor andersoni is known at present for the northwestern portion of the United States, from California to Montana; cases of rather severe lymphangitis and various swellings and sores developing from the bite of this tick have been seen by the writer. J. J. Buckley showed me quite a severe case, the patient having been bitten near the elbow; the arm became very much swollen, causing the patient to remain in bed for several days.

Dermacentor reticulatus, *D. electus*, *D. variabilis* [*D. venustus* and *D. occidentalis*, see *D. andersoni*], *Rhipicephalus sanguineus*, *R. simus*, *Rhipicentor bicornis*, *Boophilus annulatus*, *B. decoloratus*, *Hyalomma aegyptium*, *Amblyomma dissimile*, *A. americanum*, *A. cayennense*, *A. dissimile*, *A. hebraeum*, *Ixodes ricinus*, *I. r. scapularis*, *I. pilosus*, *I. bicornis*, *I. putus*, *I. rarus*, *I. cavipectus*, *I. hexagonus*, *Argas brumpti*, *A. vesper-tilionis*, *Ornithodoros moubata*, *O. coriaceus*, and *O. parmentosus* are also reported as ectoparasitic on man.

Treatment.—Ticks not infrequently hang tenaciously to the skin, but if they are covered with oil or vaseline, thus closing their breathing-pores (situated back of the fourth pair of legs), they release their hold more easily. If pulled too roughly, the capitulum ("head") is likely to break off and remain in the skin.

Sarcoptic Acariasis.—**Sarcoptic Itch.**—**Geographical Distribution.**—Judging from present records, this infection is almost cosmopolitan.

Zoölogical Distribution.—In the species *Sarcoptes scabiei*, zoölogists recognize a number of different varieties peculiar to different animals. In some cases the mites are intertransmissible between man and animals, and it is not an easy matter to distinguish between the different varieties.

The Parasites.—*Sarcoptes scabiei*,² as it occurs on man, is whitish-yellow, round to oval, with transverse rows of small spines and a number of longer bristles. In the female, both the third and fourth pairs of legs are armed with long setæ; in the male, the third pair of legs possesses setæ, but the fourth pair has a sucking-disk. The male measures 0.2 to 0.3 by 0.145 to 0.190 mm.; the female is 0.33 to 0.45 by 0.25 to 0.35 mm. The parasites bore irregular galleries, 0.5 mm. to 4 or 5 cm. or more in length, in the epidermis, especially on portions of the body where the skin is thin and soft, as on the flexor surface of the carpus, between the fingers, in the groins, at knee and elbow, on penis, breast, etc., or at points subject to pressure, as at the waistband. The female is found at the blind end of the gallery; she deposits her eggs (15 to 50 in number) and feces as she progresses. The eggs measure 140 μ and hatch in four to eight days; the parasite becomes mature twenty-eight days after birth. The male dies shortly after copulation. The fecundity is very great. This species is slightly transmissible to horses, dogs, goats, and apes, but not to cats.

Sarcoptes scabiei crustosae Fürstenberg, 1861, is associated with Norwegian itch. There is a difference of opinion as to whether this represents a distinct variety, or the ordinary itch-mite, or the itch of the wolf, which has been transmitted to man. It leads to a more severe condition

¹ See especially Railliet, 1893 a.

than the ordinary form of itch. *S. s. equi* may be transmitted to man but the infection is short-lived—about three to eight weeks. *S. s. oris* has been transmitted from sheep to man. *S. s. caprae*, of goats, may be transmitted to man and spread from man to man. *S. s. cameli*, of the camel and dromedary, may cause a severe and persistent itch when transmitted to man. *S. s. aucheniae*, of the llama, also causes a rather serious itch on man. *S. s. suis*, of hogs, sometimes attacks man. *S. s. canis*, of dogs, when transmitted to man, may be temporary or more permanent; the symptoms are similar to those caused by *S. scabiei*. *S. s. vulpis*, *S. s. leonis*, *S. s. wombati*, and *S. minor cati* will all develop on man, that of the cat most easily, but it does not persist.

Source of Infection.—Infection takes place directly from person to person through prolonged contact, indirectly through bedclothes, towels, clothes, etc., or in other cases by handling animals.

Frequency.—Itch seems to be decreasing in frequency. It increases during and immediately following a war. It is more especially a disease of the ignorant classes, but may appear in well-to-do persons. In some localities it is exceedingly common, and in others it appears especially among soldiers, sailors, laborers, shoemakers, and prisoners. Bulkley reports it in slightly less than 1 per cent. on 10,000 skin cases in private practice; and the American Dermatological Association, in 4.05 per cent. of about 200,000 skin cases. The writer finds it very common in certain rural districts.

Duration.—As successive generations develop in the skin, the untreated condition is not limited by the longevity of a single generation, but is potentially indefinite. It may last for years or even decades; it may disappear temporarily but not completely. Spontaneous cure is said to be unknown.

Symptoms.—The penetration of the mites (namely, in forming the galleries or burrows) causes an intense itching which leads to scratching, and increases under influence of heat, exercise, and especially when the patient is in bed. Various eruptions appear; papules, vesicles, and pustules form. The galleries may be white, but, because of the presence of eggs and acarine excrement, they usually become grayish to blackish; these galleries are not equally distinct in all cases. Vesicles are usually present and vary in number; they appear early in the same localities as the galleries; they are transparent at the summit, rose-colored at the base, and contain a limpid fluid; in time they dry and form a small, thin, yellowish crust; but if scratched they may become pustular. The papules appear at various places on the hands, arms, etc., and are the seat of intense itching; they rapidly increase in number, but rarely attack the face. It is stated that in 99 per cent. of cases in men lesions are found on the penis, and in 99 per cent. of cases in women, on the breast, around the nipple.

The action of the parasites is both mechanical, in tunnelling through the skin, and chemical, as shown experimentally by Delafond and Bourguignon and by Hardy. Additional injury is of course incurred by scratching; sleep may be seriously disturbed by the itching; fatal cases seem to be unknown.

Norwegian itch (*scabies crustosa*) is reported for Norway, Germany, Austria, France, Denmark, Russia, Turkey, and the United States, but is rare. It is characterized by the development of adhesive yellowish or grayish crusts, in which numerous mites are found in irregular galleries. On the palms, soles, and knees, these epidermic callosities develop 1 to 6 mm.—even 12 to 30 mm.—in thickness; they may also form on the head; the hair falls; the nails thicken and become like claws, reaching 20 mm. in thickness in some cases. Cases of Norwegian itch are of long standing, three to sixteen years, and in very slovenly people. Treatment must be prolonged and energetic.

Diagnosis.—The affection is recognized from the presence of the galleries with the female at the end. These become more distinct if the part is washed. In case of doubt the parasite or its eggs may be recognized microscopically.

Treatment.—In treatment two essential points should be considered: (1) To prepare the skin so that an acaricide can act; (2) to apply the acaricide. Various modifications in technique are adopted; the following may be taken as a radical guide, to be modified according to facilities and according to the delicacy of the skin or condition of the patient:

1. The patient, stripped naked, is energetically rubbed all over (except the head) for twenty minutes with green soap and warm water.
2. He is then placed in a warm bath for thirty minutes, during which time the rubbing is continued.
3. The parasiticide (see below) is next rubbed in for twenty minutes and is allowed to remain on the body four or five hours; in the meantime the patient's clothes are sterilized, to kill eggs or mites attached to them.
4. A final bath is taken to remove the parasiticide.

In treating thousands of cases of acariasis (particularly the psoroptic form) in domesticated animals, it is common experience that, whatever acaricide is used, much better results are obtained if it is applied as hot as can be conveniently borne. It is also common experience that while acaricides kill the mites, they cannot be depended upon to destroy the eggs; hence, time (about ten days) is allowed after the first treatment for the eggs to hatch out, but not enough time for them to become adult and begin to lay eggs; then the treatment is repeated.

In treating itch in man, hand applications are used. Kaposi does not consider the baths and frictions necessary. He uses an unguentum naphtholi compositum prepared as follows: adipis 100.0, sapon virid. 50.0, cretæ preparatæ 10.0, naphthol 15.0. Helmerich's formula (which is very irritating to the skin) is: sulphuris sublimat. 10.0, potass. carbonat. 5.0, aqua dest. 5.0, ol. amygd. dul. 5.0, adipis 35.0. Bourguignon's ointment is composed of: ol. lavand., et menthæ, et caryophyll., et cinnamomi, each 2.0, gumm. tragacanth. 5.0, potass. carbonat. 30.0, flor. sulph. 90, glycerin, 180.0. Hebra's modified Wilkinson ointment is made of: flor. sulph. et ol. cadini, each 180.0, adipis et sap. virid., each 500, cretæ preparatæ 120.0.

Demodectic Acariasis.—Infection with the hair-follicle mites.

Geographical Distribution.—Exact data on this point are lacking, but the infection is probably more or less cosmopolitan.

Zoölogical Distribution.—The hair-follicle mite, *Demodex folliculorum*, is reported not only for man but also for quite a number of animals, as dogs, cats, horses, cattle, hogs, etc. The forms which attack animals are usually considered specifically identical with that which attacks man, but as representing distinct varieties. There is some doubt at present regarding the intertransference of these varieties between animals and man; if such infection does occur it seems to be rare. The infection in dogs is the classical example of the disease; it is very difficult to cure, and quite fatal. In cattle the infection is of considerable economic importance from its effect upon the hides.

The Parasite.—*Demodex folliculorum*,¹ as found in man, is an elongate, worm-like mite, 300 to 380 μ long by 40 to 45 μ broad, with rather short, broad rostrum, and 4 pairs of short legs. It is very common in the sebaceous glands of the face, alæ of nose, lips, cheeks, forehead, Meibomian glands, and is also found in the cerumen, ventrum, dorsum, hair follicles of the chest, and at the root of the pubic hairs. In healthy glands only a few (one or two specimens) are found, but the number may increase to 15 or 20 or even many more; usually the head is toward the bottom of the follicle. This parasite multiplies very slowly, passing through the stages of egg, hexapod larva, octopod nymph, second nymph, and adult. It may live six or more days after the death of the host.

Source of Infection.—So far as known, and judging from analogy, infection may be direct or indirect from person to person.

Frequency.—Guiart (1902*b*) has found this parasite in all cases in which he has looked for it; Gruby found it in 40 out of 60 persons examined. It is apparently much more common in adults than among children.

Duration.—The longevity of the individual parasite is not established, so far as known to the writer, but judging from the life-cycle of the parasite a case of infection is potentially indefinite.

Symptoms.—That the effect of the hair-follicle mite has been both overestimated and underestimated is probably quite certain. The vast majority of cases pass unnoticed, but one case has been seen by the writer (in man) of nodular formation as large as a pea, caused by these parasites. The relation of the mite to acne is *sub judice*; that they may be one cause of acne seems, *a priori*, probable.

Treatment.—Several authors intimate that these parasites are easily killed, but in view of the difficulty experienced in treating the affection in dogs, etc., a question regarding the correctness of the interpretation in the cases in man, naturally and legitimately arises.

OTHER FORMS OF ACARIASIS

Of the numerous other mites reported for man, probably the most important for this country are:

The harvest mites (*Leptus americanus* and *L. irritans* Riley; *L. autumnalis* Shaw, 1790, is a European species), also known as the "red bug" or "harvest bug," or occasionally as the "jigger." These are

¹ SYNONYMS.—*Acarus folliculorum* Simon, 1842; *Demodex folliculorum* Owen, 1843; *D. folliculorum hominis*.

hexapod larvæ of mites, of the genus *Trombidium*. They attack man in the fields in summer and burrow into the skin, causing a very irritating sensation, and even a considerable amount of suffering, increased by scratching. The symptoms disappear after a few days.

Treatment.—A warm bath within a few hours after exposure; rub lesion with carbolized vaseline, sulphur ointment, or corrosive sublimate (2 to 1000); extraction of the parasite with a fine needle.

Pediculoides ventricosus is a minute mite that attacks persons working with infested wheat or straw, or sleeping on infested straw mattresses, and causes a condition known as straw-itch, straw-mattress itch, or dermatitis schambergi. This eruption may occur in single cases or in epidemic form, not only in wheat areas, but in localities to which the wheat, straw, or straw-mattresses are shipped. The differential diagnosis (from chiggers, scabies, and common hives) is easily made by finding the mite which has but a feeble attachment to the skin.

Within twelve to sixteen hours after exposure the first and invariable symptom, itching, appears; in severe cases, and especially when the cause is not suspected or recognized and the exposure is continued night after night by sleeping on an infested straw mattress, for example, the itching may become almost intolerable. The eruption appears simultaneously with the itching, and characteristically consists of wheals surmounted by a vesicle. The latter, as a rule, does not exceed a pin-head in size, but it may become as large as a lentil seed or pea. Its contents very rapidly become turbid, and the vesicle is converted in a few hours into a pustule. Instead of frank wheals there may be erythematous or papulo-urticarial lesions, which are irregularly circular or oval in outline, from a lentil to a finger nail in size, and usually of a warm rose tint. The pinkish-white anemic area of ordinary "hives" is rare. The eruption is most abundant on the trunk, slight on the face and extremities, and practically absent from the feet and the hands. Even when experimentally exposed to attack, the limbs, for some reason, largely or altogether escape. The onset in severe cases may be marked by chilliness, nausea, and vomiting, followed for a few days by a slight elevation of temperature with the appearance of albumin in the urine. In the less severe types there may be only some diminution of appetite and malaise, or a constitutional reaction may be altogether absent.

As has already been indicated, *P. ventricosus* does not bore into the skin. Its attachment to the surface being feeble, it is readily brushed off by the friction of the clothes; local antiparasitic treatment is therefore hardly necessary. If desired, however, a mild sulphur ointment will answer this purpose. Antipruritic treatment is always called for; warm, mildly alkaline baths or some simple soothing ointment, such as zinc oxide, will be found to fulfil this indication. Of course, contact with the suspected straw or grain must be discontinued. The clothes and body linen must be changed, but as the mite cannot survive more than a day without food, airing them for a day or so will be sufficient to free them from danger.¹

¹ See especially Goldberger, 1910, *Public Health Reports*, June 10, pp. 779 to 784.

Trombidium tlalsahuatl (Lemair, 1867) occurs in Mexico, and attacks the eyelids, axillæ, navel, and prepuce, causing itching, redness, swelling, and even pus-formation; symptoms usually disappear in about a week.

The **kedani mite**, *Tr. "akamushi,"* is a Japanese acarine supposed to be connected indirectly with "river fever;" the bacterium associated with the disease is supposed by Takana (1889) to enter through the puncture in the skin made by the mite.

Tetranychus molestissimus occurs in South America.

Tydeus molestus Moniez, 1889, was probably imported into Belgium with Peruvian guano. It also attacks man.

Chicken mites (*Dermanyssus gallinae*), and a closely allied species (*D. hirundinis*) from swallows, may attack man, causing a cutaneous eruption with considerable itching.

Holothyrus coccinella Gervais attacks birds, especially ducks and geese, in Mauritius; it attacks man, causing a cutaneous swelling with a burning sensation; it is said to enter the mouth of children.

Various mites are accidentally swallowed in food (cheese, etc.) or water and are found in the feces. Among the acarines reported for the feces may be mentioned *Glyciphagus domesticus* (de Geer) and *G. prunorum* (Her); the former causes a condition known as "grocers' itch."

Tyroglyphus farinae (de Geer) attacks men handling grain; *T. longior* (Gervais, 1844) and *T. siro* (Linnaeus) are reported as occurring on man or in the urine and intestine.

Histiogaster spermaticus Trouessart, 1900, is a mite reported as having been found in a cyst in the testicles; it may possibly have gained access by being introduced into the urethra in catheterizing.

Necrophagus sanguinari Miyake and Scriba, 1893, was found dead in the urine in a Japanese case of fibrinuria with hematuria and chyluria; it was supposed to have come from the kidneys, but there is room for grave doubt concerning this point.

Mention may also be made of the following: *Acaropsis mericourti* (in ear); *Carpoglyphus alienus*; *Cheyletus eruditus* (in ear); *Histiogaster entomophagus*; *Laelaps stabularis* (causes pruritus); *Liponyssus sylviarum* (causes intense pruritus); *Metatrombidium poriceps*; *Microtrombidium (meridionale, pusillum, wichmanni, vandersandei)*; *Rhizoglyphus parasiticus* (India, in ground itch); *Tarsonemus intectus* (Danube valley); *T. hominis* (in an ovarian tumor); *Tetranychus telarius*.

POROCEPHALIASIS OR TONGUE-WORM INFECTION

At least three species of tongue worms (*Linguatulidae*) are known to occur in man. They are not true worms, but belong to the arthropods. They are not especially dangerous.

Linguatula serrata Frölich, 1789, measures 18 to 20 mm. (male) long by 3 to 4 mm. broad, and 8 to 13 cm. (female) long by 8 to 10 mm. broad. The adult stage inhabits the nasal passages of canines, while the larvæ, which measure only 4.5 to 5.5 mm. long, are encysted in the liver, lungs, etc., of rabbits, cattle, sheep, and various other animals. Both the larval

and the adult stages are recorded for man, especially in Europe. The larva has been found also in American cattle and rabbits. In cases of nasal infection with gravid females, the diagnosis may be made by finding the four-legged embryo, enclosed in its egg-shell, in the nasal discharge; diagnosis of infection by the encysted larva is made post-mortem.

The larva of *Porocephalus armillatus* (Wyman, 1847) is reported as encysted in various organs of man in Africa. The adult lives in the lungs of the Royal Python and of other snakes. *Pentastomum constrictum* (also reported for man) is viewed by Sambon as identical with this species. The larval parasite is encysted in various organs.

The larva of *Poroc. moniliformis* (Diesing, 1836) is reported for man in Asia and Africa, but Sambon views the African cases as coming under the foregoing species. The adult is found in the lungs of various snakes (*Python reticulatus* and others). In a case reported for Africa by Broden and Rodhain (1909) the infection was generalized; Seiffert (1910) found 17 cases of infection in 218 autopsies in Kamarun. Raebiger (1910) reports an African case of porocephaliasis in which the infection extended to the brain. In both *armillatus* and *moniliformis* infections, man is only an accidental host; the larval forms are found also in various monkeys, rodents, etc. For compilation of cases in man see Sambon, 1909 and 1910, *Jour. Trop. Med. and Hyg.*

MYRIAPODA

The myriapods are not true parasites in man, but occasionally, they are found as accidental parasites in the nose or intestine. Blanchard (1898c) collected 35 such cases. The species thus far reported in such cases are: *Scutigera coleoptrata*, *Lithobius* (*forficatus* and *melanops*), *Geophilus* (*carpophagus*, *electricus*, *similis*, and *cephalicus*), *Himantarium gervaisi*, *Chaetechelyne resuviana*, and *Haplophilus subterraneus*.

PARASITIC INSECTS¹

Adult insects have 6 legs, and, usually, 2 or 4 wings. The larvæ are more or less worm-like, and are known as "grubs," "bots," etc. Both the larval and the adult stages may be parasitic. They are of more importance in medicine as transmitters of disease (mosquitoes and malaria, yellow fever, and filariasis) than they are as parasites (fleas, lice, grubs, etc.), and we may lay down the *general* rules that diseases (such as malaria, filariasis) which are dependent upon insects and other arthropods for their distribution, are caused by animal parasites, while those (such as typhoid) which may be disseminated by arthropods, but are not dependent upon them, are usually caused by plant parasites.²

Burrowing Fleas: Jigger Flea, Chigger or Chigoe.—Geographical Distribution.—This is a tropical and subtropical parasite of American

¹ See especially Osborn, 1896, "Insects Affecting Domestic Animals," *Bull.* 5, n. s., *Div. Entomol., U. S. Dept. Agric.*, Washington.

² Whether the African tick fever and the Rocky Mountain "spotted fever" form exceptions to these rules is a point for further study.

origin; it has now been introduced into Africa and adjacent islands, where it has spread rapidly; it is also reported for Persia, India, and China.

Zoölogical Distribution.—This parasite attacks not only man, but also horses, cattle, swine, and dogs. It is said to attack chickens and certain other birds; but, as a distinct species (*Argopsylla gallinacea*) is found on chickens and also reported as attacking man, it might be well to reëxamine this infection to see whether a confusion in determination has occurred.

The Parasite.—*Sarcopsylla penetrans*¹ (Linnaeus, 1758) is about 1 to 1.2 mm. long; when young, the female resembles other fleas, but, after mating, it burrows into the skin and swells into a body resembling a beet in appearance. The female remains in the skin about three weeks. The males do not burrow. The eggs hatch out on the ground and the larvæ undergo a resting stage.

Frequency.—In some localities this infection is very common. Manson reports that it causes a large amount of invalidism among the coolies in East Africa. There may be only one or two parasites present, or the fleas may be so numerous and thickly set as to give the infected part a honey-combed appearance.

Symptoms and Pathology.—The fertilized female burrows into the skin, especially on the feet, but also on other portions of the body, forming small, pea-like, elevated swellings; the caudal end of the flea may be seen at the opening of the burrow. The parasite causes considerable irritation; pus forms around it; the skin may ulcerate, leaving a sore.

Diagnosis.—The diagnosis is not difficult. The pea-like swellings on the feet, especially under the nails and between the toes, are in themselves suspicious, and a closer examination reveals the parasite.

Treatment.—The entire parasite should be pried out with a sharp knife or similar instrument, when possible without breaking. Application of chloroform, or mercurial ointment may first be used to kill the flea. The wound is thoroughly cleansed and dressed.

Prevention.—The wearing of shoes in the infected districts will greatly reduce the chances for infection.

Jumping Fleas:² *Pulex* and *Ctenocephalus*.—**Geographical Distribution.**—Cosmopolitan.

Zoölogical Distribution.—Fleas are common on numerous different species of animals, and some of the species are intertransmissible between man and their normal hosts.

The Parasites.—There are two fleas in particular which attack man: *Pulex irritans* (Linnaeus, 1758), known as the "house flea" or "common flea," is more common in Europe than in the United States.

Ctenocephalus canis (Curtis, 1826), the ordinary "cat and dog flea," seems to be more common in the United States than *P. irritans*; it differs from *P. irritans* in the presence of a comb-like structure on the

¹ SYNONYMS.—*Pulex penetrans* Linnaeus, 1758; *Sarcopsylla penetrans* (Linnaeus) Westwood, 1840.

² For a zoölogical revision of the fleas, with a list of all species on various animals, see Baker, 1905, Proc. U. S. Nat. Mus.

first thoracic segment. The flea-eggs develop in cracks in the floor and other suitable places. In the case of *C. canis* the egg stage lasts one day, the first larva, three to seven days, second larva, three or four days. They commence spinning from seven to fourteen days after hatching, and the imago appears five days later; thus an entire generation may develop in a little more than a fortnight.

Medical Importance.—Adult fleas may: (a) attack man as ectoparasites; (b) act as intermediate host for certain tapeworms (*Dipylidium caninum*, see p. 255); (c) act as disseminators of plague. Flea-larvæ are also reported as pseudoparasites in man.

Prevention.—Many methods are suggested to protect against the attacks of fleas, as, for instance, the use of essential oils; but the reports from their use are not very encouraging. It is better to clear the fleas out of the house by fumigation with sulphur, by sprinkling pyrethrum powder, or by washing the floor with benzine or hot soap-suds.

Pediculosis: Lousiness.—There are three species of lice which attack man: namely, the head-louse, the body-louse, and the pubic-louse.

Geographical Distribution.—Cosmopolitan.

Zoölogical Distribution.—The three lice typical for man do not normally live on other animals; occasionally lice from various animals attack man, but remain on him only a short time.

The Parasites.—The head-louse (*Pediculus humanus*¹ Linnaeus, 1758) lives among the fine hairs of the head; the female lays 50 to 60 eggs or “nits” within six days; these white “nits” are attached to the hair, especially back of the ears; they hatch on the sixth day; the young become mature in seventeen to twenty days.

*Pediculus corporis*² de Geer, 1778, the body-louse, secretes itself in the folds of clothing, but draws its food from the body; it lays 70 to 80 eggs in the folds of the clothing; these hatch in three to four days and mature in fifteen to eighteen days.

The pubic-louse, or crab-louse, *Phthirus pubis*³ (Linnaeus, 1758) is much more common on men than on women; it is found chiefly on the pubes, occasionally on the eyelashes, and is reported also for the head. It lays 10 to 15 eggs, which hatch in six to seven days and become mature in fifteen days.

Source of Infection.—Lice may pass directly from one person to another or may be carried by flies. Beds are also sources of infection.

Symptoms.—Head-lice may cause an irritation accompanied by an eczema or pustular dermatitis. The discharge, mixed with excoriations due to scratching, mats the hair together; scabs and crusts form; if allowed to run, a regular carapace may form, called *trichoma*, and the head exudes a fetid odor. Various low plants may grow in the trichoma, the entire structure being known as the *plica polonica*.

Body-lice cause rose elevations, analogous to urticaria, and papules which become excoriated at the summit and covered with brownish

¹ SYNONYMS.—*P. capitis* de Geer, 1778; *P. cervicalis* Latreille, 1803.

² SYNONYMS.—*P. vestimenti* Nitzsch, 1818; *P. tabescentium* Alt, 1824.

³ SYNONYMS.—*P. pubis* Linnaeus, 1758; *P. inguinalis* Reichard, 1759; *Phthirus inguinalis* (Reichard) Leach, 1815; *P. pubis* (Linnaeus, 1758) Küchenmeister, 1855.

crust; itching and scratching result, and white scars are found, surrounded by brownish pigment; the skin may become thickened and takes on a bronzed tinge, presenting a melanoderma which is one of the chief attributes of vagabonds' disease.

Pubic-lice cause an irritating pruritus, especially at night; a dry prurigo, represented by small rose or reddish papules; and in some cases in the subumbilical region, on the flanks and internal surface of the thigh, bluish-gray temporary spots, 7 to 8 mm. in diameter, not painful and not paling much on pressure.

Treatment.—If feasible, as in male patients, it is well to cut the hair, although this is not at all necessary. Saturation of the head with kerosene emulsion will kill the lice, but carbolic washes are more severe on the eggs ("nits"). Washing with tincture of *Cocculus indicus* is advised by some authors, its advantage being the absence of odor. The same measures may be used for the pubic-louse; or mercurial ointment may be applied. In treating the body-louse, it is the clothes more than the body which need radical treatment. The entire clothing should be baked or boiled. The itching may be allayed by warm baths, sodium bicarbonate being added to the water.

Bed-bugs.—**Geographical Distribution.**—Cosmopolitan.

Zoological Distribution.—The popular view that bed-bugs are carried by swallows and bats is erroneous; generically identical but specifically distinct parasites infest these animals.

The Parasite.—There are two bed-bugs which infest dwellings in this country. The "common bed-bug," *Cimex lectularius* Linnaeus, 1758, does not require description. It is a very intelligent animal, which secretes itself in crevices, in cracks, in draperies, and around the buttons of mattresses during the day, seeking its food at night. It lays eggs from which the larval stage issues; in its development it sheds its skin, and it feeds once between every two moultings, then once again after the last moult before it lays its eggs.

The Mexican bed-bug, or blood-sucking cone-nosed bug (*Conorhinus sanguisuga*), is spreading from Mexico toward the North. The adult possesses wings. This is normally a predaceous insect rather than a parasite, and it feeds upon the bed-bug. Having tasted human blood from this source, it is now acquiring the habit of attacking man.

Source of Infection.—Bed-bugs wander from house to house, but they are usually spread through the moving of old bedding, or in clothes. The laundry is a common source of importation, especially in localities like Washington, where negroes take the laundry to their homes.

Symptoms.—The writer is convinced that the common bed-bug may occasionally be of greater medical importance than is usually attached to it. He knows, for instance, of one case where a young man underwent treatment for neurasthenia; all symptoms promptly disappeared, however, immediately following a thorough fumigation of his rooms, where nearly a pint of bed-bugs was collected. The effect of bed-bugs upon delicate or young children, in loss of sleep, is occasionally a matter not to be entirely ignored; this is a point of importance in many families in certain factory and rural districts, but it is too frequently overlooked.

Treatment.—This consists in removing the cause. Above all methods, the writer favors thorough fumigation of the house with flowers of sulphur (2 pounds to 1000 cubic feet of space). For practical reasons, in order not to attract attention, it is best to start the fumigation in the evening after dark. In experiments in Washington, and in New Jersey, he has generally placed ordinary powdered sulphur in wash-basins, old kettles, etc., and set these dishes on bricks in larger basins or tubs containing water enough to come close to the top of the dish containing the sulphur; a small well is made in the sulphur with the finger and a small amount of alcohol poured in; the alcohol is then set on fire and the sulphur allowed to burn out. All windows should be tightly shut, and the room should remain closed for twelve to twenty-four hours. Metal ornaments, clocks, valuable tapestries, etc., should be removed before fumigating.

The treatment with hydrocyanic-acid gas is too dangerous and too expensive for general adoption, especially among the poorer and more ignorant classes, as the fumigation is usually carried out by women in the family, who in their haste to leave the room when the gas is started may trip on their dresses; fatal accidents might occur, quite aside from the injury done to rugs, etc. The sulphur fumigation does not present this danger. The ordinary methods of washing with kerosene, gasoline, etc., are good so far as they go, but are less reliable than thorough fumigation with sulphur. A saturated solution of corrosive sublimate in water may be used in the cracks of wooden beds, floors, etc.

Myiasis.—**Dipterous Infection.**—The term "myiasis" is used to denote an infection with the larval ("grub") stage of dipterous insects. Various authors distinguish a *Myiasis externa* and *interna*, *M. intestinalis* and *dermatosa*, or *M. oestrosa* and *muscida*, the first four terms being based upon the position of the parasites, the last two on the zoölogical classification. For American physicians, the most important is the—

Screw-worm.—*Comptosmyia macellaria* is a fly which deposits its eggs in wounds. It may also oviposit in the nostrils of persons (particularly those with offensive catarrh) when sleeping out of doors. The larva, known as the "screw-worm," issues within a few hours, and burrows into the tissues; it feeds for five or seven days, then exits to pupate. Accordingly, in case of infection the larvæ continue their active injury for five to seven days. Infection with this larva may be serious, and in a high percentage of the cases (21 in 31, Maillard) fatal. An effort should be made to kill the larvæ by douching with a 20 per cent. solution of chloroform in sweet milk, or a carbolic wash; some of the parasites may be removed with simple salt water, or with forceps. Various larval insects are also found in fresh wounds, and have been especially troublesome in time of war.

Scoleciasis.—Scoleciasis is a term used to designate accidental infection with coleopterous larvæ. *Necrobia* sp. has been reported for the eye.

Miscellaneous.—The reported cases of snakes, frogs, earthworms, etc., as parasites are instances of spurious parasitism.

PART III

DISEASES CAUSED BY PHYSICAL AGENTS

CHAPTER VIII

LIGHT, X-RAYS, ELECTRICITY, AIR, HEAT, AND COLD

By ALFRED GORDON, M.D.

LIGHT

Physiological Effects.—Light belongs to the category of objects without which both plant and animal life are impossible. The favorable effect of light and chemical rays of the sun upon animal life has been known from most ancient times. The Italian proverb, "All diseases come in the dark and get cured in the sun," is very significant. Physiology and observation show that the respiratory chemistry, formation of hemoglobin in the blood, growth of the organism, and pigmentation of the skin, are directly dependent in a large measure upon light. Finally, functions of various glands and metabolism in general are undoubtedly in some relationship to light. Forbes Winslow has shown the effect of light on the growth of man. Growth of children during the months poor in sunlight is slow; this is particularly noticeable in children of the poor who live in basements.

Besides the direct physiological effect on the functions of the organism, light has also a beneficial effect upon the nervous system and psychic sphere. Disposition, humor, and general sensations are more agreeable in a clear, sunny day than in cloudy and gloomy weather.

Nature has provided us with light also as a means of defence against pathogenic microbes. The favorable results obtained in the treatment of pathological conditions of the skin, according to Finsen's method, are perhaps due to its effect upon microorganisms. The action of light is probably due to the permeability of the skin and other tissues. Bouhard has shown that it is principally the ultraviolet rays that penetrate the tissues; the reflex stimulation is then transmitted through the skin and from the latter to the central nervous system, which in its turn influences various organs.

Pathological Effect.—If moderate light has a favorable influence on the entire organism, intense light, on the contrary, acts unfavorably. The degree of injury naturally depends upon the intensity of and length

of exposure to sunlight. Locally one may observe *sunburn*, which in mild cases is manifested in a simple erythema, and in severe cases in an inflammation with swelling and even destruction of skin. Freund, among others, has shown that in such cases a large number of ultra-violet rays traverse the epidermis and reach the deep layers of the skin, in which they affect the cellular elements. When œdema and exudation, with subsequent destruction, take place, a general reaction, with elevation of temperature, will follow. In extremely severe cases, when destruction is extensive, internal complications may ensue. In ordinary cases of sunburn, pigmentation may occur; the latter is, according to Finsen, a natural protection against further effect of light rays.

Exposure to sun rays may be an exciting cause for various affections of the skin in predisposed individuals. Lentigo, for example, is the well-known freckles, which appear usually on the face, neck, and hands; they disappear almost entirely during winter and reappear in summer. Chloasma, xeroderma pigmentosum, and hydroa are cutaneous affections in which sunlight plays a certain rôle as a causative agent. The skin is not the only organ which may suffer from the immediate effect of intense sunlight. The eye may become affected. Ophthalmia and conjunctivitis are not infrequent in the polar regions and in the mountains. A few cases were reported in which cataract was apparently produced in workmen whose eyes were exposed to prolonged action of intense light.¹

All these changes, and particularly those of the skin, are the result of the effect of light rays in a comparatively mild degree. The produced lesions are usually limited to the tissue exposed to the light. When the effect of intense sunlight is manifested in general disturbances, the condition may become alarming, as it may terminate by death. We speak then of sunstroke.

The term "sunstroke" has been considerably abused. Heat-exhaustion, heatstroke, sunstroke, insolation, coup de soleil, heat-asphyxia, and thermic fever have been described as one condition. Manson, in his book on *Tropical Diseases*, brings some order in the terminology, and his classification is satisfactory. He considers separately a condition produced by the elevated temperature, to which he gives the name "heat-exhaustion;" another condition produced apparently and only by the direct rays of the sun, to which he gives the name "sun-traumatism;" and, finally, a third morbid state, to which Sambon gave the name "siriasis." The latter is in all probability due to a microorganism which develops only in a high atmospheric temperature.

1. **Heat-exhaustion.**—This is characterized by a sudden tendency to syncope in an atmosphere with a high temperature. It can be brought on indoors or outdoors. The main etiological factor is heat from any source. It is observed in industrial plants where work is carried on at temperatures above 120° F. Individuals suffering from various diseases, those whose physiological activities are lowered by alcoholic or other excesses, or by exhaustion, present very little resistance to the effect

¹ Wm. Robinson, *British Medical Journal*, January 24, 1903.

of heat. With the syncope occurring from heat-exhaustion are also observed the following symptoms: shallow respiration, small and soft pulse, dilated pupils, cold skin, and subnormal temperature. Recovery usually follows, but very occasionally death may ensue.

Heat-exhaustion brought on by exposure to the sun is called sunstroke, insolation, or coup de soleil. This condition is of great interest, especially to military surgeons; insolation in the army during summer months is of frequent occurrence. In warm climates those who are compelled to work outside of dwellings are apt to be stricken. Those who use alcohol are particularly predisposed to the effect of intense heat, and they constitute the majority of the victims of sunstroke. Some individuals are peculiarly predisposed to repeated attacks. Four cases came under the writer's personal observation, in which the patients, free from alcoholism, had three attacks during three successive summers. Among other predisposing causes we may mention excesses of all kinds, constitutional diseases, or low vitality following protracted diseases. Finally, any cause which prevents the evaporation of the perspiration, as, for example, clothing fit only for cold weather and worn on hot days, predisposes to sunstroke. It is interesting to note that the black race is remarkably resistant to the effect of intense sunlight. Cases of insolation in children are also rare.

Sunstroke (Insolation).—*Symptoms.*—In the majority of cases a sunstroke is preceded by a few premonitory symptoms before complete prostration sets in. They are headache, dizziness with generalized tingling sensations, and nausea. Pain in the epigastrium, vomiting, and excessive thirst soon make their appearance. Consciousness is retained in mild cases. The patient enters into a state of exhaustion, which may go to complete prostration and end in death quite rapidly. If he survives, a slight fever may be present, which gradually goes down to normal. The above-mentioned symptoms then gradually subside and complete recovery takes place. Before recovery occurs the patient will complain for a long time of headache; this is practically the only symptom which persists after others have disappeared. In severe cases of insolation there is always a loss of consciousness, which may be followed by death; the latter is rather exceptional. In a great majority of cases the patient regains consciousness; but there is extreme pallor, rapid respiration, rapid pulse, which is soon succeeded by a slow pulse; temperature is raised to 104° or 105° and in very severe cases to 108° . In some cases the temperature reached 112° to 113° , which, according to certain observers, is not uncommon in severe forms. The skin is usually dry or covered with a clammy perspiration. Convulsions, epileptiform in character, may occur, while general muscular twitching is exceedingly common. Delirium is not an infrequent occurrence. The entire body is either in a state of rigidity or absolute flaccidity. Ecchymosis, or a petechial rash, is observed in a certain number of cases.

The severity of certain cases is not dependent upon the degree of the temperature or upon the state of the pulse, and it is therefore difficult to foretell exactly the issue of a given severe case. Despite the unusually pronounced symptoms, recovery may follow, although not without a

persistent headache and various paresthetic disturbances, as tingling, numbness, pins, and needles, etc., or some physical and intellectual weakness. Generally speaking, patients who remain unconscious for twenty-four or forty-eight hours usually die.

Sunstroke is one of the causes of chronic meningitis, and the cephalæa which so frequently follows recovery from insolation finds its explanation in the meningeal involvement. Far more important and frequent sequelæ of sunstroke consist of distinct mental disturbances, as impairment of memory or of sustained attention. Some writers pretend that delusional insanity, paresis, and mania may be caused by insolation. The writer's view is that if insolation is sometimes followed by these mental derangements, it is only as an exciting cause similar to trauma; patients of this character undoubtedly were predisposed to insanity or were already insane, and exposure to intense sun radiation only intensified the condition. Among other possible consequences of sunstroke we may mention polyuria and glycosuria.

Pathology and Pathogenesis.—The gross pathological changes may be expressed in one phrase: general congestion of the organs. The lungs, liver, spleen, and particularly the meninges of the brain and cord, are in a state of congestion. The blood is very fluid. The microscopic studies of various tissues and organs show that the cells of the liver and kidneys and of the nervous system all undergo parenchymatous degeneration. The nervous system suffers particularly, and there the changes are similar to those found in cases of intoxication with poisons, as lead or alcohol: namely, marked chromatolysis of the cells. The condition of the blood deserves special attention. Leukocytosis and in some cases destruction of erythrocytes with diminution of the alkalinity of the blood are the changes which occur.

As to the pathogenesis, there is a great divergence in the theories which have been advanced. Vallin at first believed that death was due to heat coagulation of the cardiac muscle. Hirsh believes that the cause of death was in alteration of the blood—diminution of oxygen and retention of a toxic principle. Vincent¹ arrived at the conclusion that there is a poisoning of the organism by toxic products accumulated in the blood. According to Laveran and Régnard,² who made an extensive experimental study of the question, death is due to a direct effect of sun rays, principally upon the nervous system; this effect is first excitant and then paralyzing. More recent investigations tend to the conception of a paralyzing action on the nervous system of some toxic element, with the probable result of metabolic changes in the neurons; and according to the degree of intoxication the result is either an attack of ordinary heat-prostration or syncope with unconsciousness or death.

Diagnosis.—It is only in exceptional cases that this is difficult. Usually the history of exposure, with the high temperature and the condition of the skin, render the diagnosis easy. In some cases, especially when there is a history of alcoholism or cardiac lesion, the diagnosis will be difficult; apoplexy should then be thought of. In the latter case the

¹ *Rech. exper. sur l'hyperthermie*, 1887.

² *Bull. d. l'Acad. de Méd.*, 1894.

temperature is usually normal, the breathing is stertorous, the pulse is slow; but the most important symptom is the local paralysis, hemiplegia, or monoplegia. In malarial districts, a pernicious malarial paroxysm may give difficulty, but a blood examination will give the diagnosis.

Prognosis.—The outlook depends upon the degree of prostration, and, according to some authors, upon the temperature. The latter condition is not absolute, and the writer has observed a patient with 110° who recovered. However, on general principles a very high temperature renders the prognosis unfavorable. The previous general health, and especially whether the patient uses or does not use alcohol, is of utmost importance in forecasting the outcome. The promptness of assistance and the character of the treatment are factors which play an important rôle in determining the prognosis. In mild cases of heat-prostration the prognosis is favorable. As to the complications following sunstroke, they are all, as a rule, temporary, except the grave forms of insanities. As in the latter, sunstroke similar to trauma plays only the rôle of exciting factor, the prognosis will not be dependent upon the insolation. In some cases the sequelæ are very rebellious to treatment, and may persist for a long time. Finally, some patients become predisposed to repeated attacks after they have once had a sunstroke.

2. **Sun-traumatism.**—Under this name Manson describes a morbid state characterized, as a rule, by sudden death occurring without warning after exposure to the sun. Paralysis of the heart or respiration seems to be the immediate cause of death. In a certain group death may not ensue, but the patient exhibits symptoms of meningitis: namely, fever, headache, dry skin, rapid pulse, photophobia, and vomiting. The condition is not invariably fatal. If recovery follows, there are always sequelæ more or less persistent in character, as tremor, amaurosis, amnesia, deafness, epilepsy, and paralysis or paresis of the extremities.

As to the pathogenesis, it is highly probable that caloric is not at fault, as similar effects have not been observed from exposure to heat from other sources—as a furnace, for example. Manson is therefore justified in presuming that there is a special element in the solar spectrum capable of injuriously affecting the tissues, particularly if they have not become gradually habituated to sun exposure. To corroborate this view Manson calls attention to the phenomena of sun-erythema, of skin pigmentation known as sunburn, and possibly of leukoderma; also to the sensation of distress brought on by exposure to a hot sun, which is quite different from that produced by the heat of a fire.

3. **Siriasis.**—This is a specific disease developing in high atmospheric temperature, and is not caused by the elevated temperature, but probably by some microorganism which demands for its development a high atmospheric temperature and certain local conditions. It is known on the east coast of the United States and the South Atlantic coast; in Africa, Asia, and Australia. The mortality from this disease is very great. According to Manson (*Tropical Diseases*) the case mortality among English troops is about one in four. The symptoms observed are almost identical with those of sunstroke, and are characterized mainly by hyperpyrexia, coma, and extreme pulmonary congestion. If a postmortem examination is

made shortly after death and before decomposition changes have set in, the heart is found to be remarkably rigid. Rigor mortis is an early appearance. The blood is remarkably fluid and yields an acid reaction. Venous engorgement of the viscera is a notable feature.

Treatment of Heat-exhaustion, Sun-traumatism, and Siriasis.—The first indication in cases of heat-prostration, be it mild or severe, is rest. At once the patient must be undressed and put to bed; if stricken on the street, the clothing must be loosened, and he must be laid on his back in a cool, airy, and shaded place. The next indication is application of cold to the head, and some stimulant (brandy or others) administered. In mild cases this treatment will be sufficient. In more severe cases, in addition to these means, some drug may be given to alleviate the headache and reduce the high temperature. The coal-tar products, salicylates, etc., will answer both indications, but should always be used with caution. When the prostration is very pronounced and the temperature is below normal, heat instead of cold will have to be applied—in conjunction with some internal stimulant, if there is no coma; if coma, stimulants must be given hypodermically. Strychnia, camphor, and nitroglycerin are the usual drugs for the latter purpose. Convulsions can be controlled by placing the patient in a lukewarm bath and by administration of morphine aided by atropine. Restlessness and insomnia are best treated by the bromides. High temperature can be controlled particularly by cold spongings frequently repeated, or by baths, the temperature of which is gradually reduced while the patient is in the tub. The patient should be vigorously rubbed. The same procedure can be employed in cases of unconsciousness. These hydrotherapeutic measures can be modified according to the conditions in each individual case. If baths are not convenient, cold packs may take their place. Sometimes a shower-bath, or a douche over the spine, of short duration and followed by a dry rubbing, reduces the temperature admirably besides having a stimulating effect. It should be borne in mind that while the patient is treated with cold water, stimulation with the above-mentioned means should be kept up. Among the stimulants the writer lays special emphasis on saline infusions, which in many cases prove to be an excellent adjuvant. If the patient is a full-blooded individual, venesection followed by saline infusions will be of better service than infusion alone. When death is imminent, repeated stimulation with the usual remedies and artificial respiration must be used.

After the pronounced symptoms have disappeared, the treatment will be symptomatic. Headache, insomnia, nervousness, paresthetic disturbances, should be treated accordingly.

When the *hyperpyrexia* is great, all the efforts must be directed toward reducing the temperature by rapidly acting measures. Chandler's¹ directions are of great value in such cases. He advises to put the patient, undressed, on a stretcher, the head of which is raised slightly so as to facilitate the escape of involuntary evacuations and to provide for drainage. A thermometer is kept in the rectum. The body is covered

¹ *Medical Record*, New York, 1897.

with a sheet upon which is laid numerous small pieces of ice, larger pieces being closely packed about the head. Iced water is then allowed to drip for thirty to forty minutes on the patient, from drippers hung at an elevation of from five to ten feet. A fine stream of iced water poured on the forehead from an elevation will act as a stimulant; this powerful measure must not be kept up for longer than one or two minutes. A hypodermic injection of forty minims of tincture digitalis is given as soon as possible, its administration being preceded in the case of plethoric patients by a small bleeding. As soon as the rectal temperature has sunk to 104° the application of cold should be at once discontinued. On discontinuing the iced sheet, the patient should be wrapped in a blanket and hot bottles applied to limbs and trunk. In this stage strychnia as a stimulant should be avoided. In case of failure of respiration, artificial respiration should be resorted to. Chandler urges to keep it up for half an hour. There is a very important warning given by Manson. Antipyretics (antifebrine, antipyrine, etc.) should by all means be avoided, as they are dangerous in view of their depressing action on the heart.

Prophylactic measures are of greater importance. The investigations of Laveran and Régnard, also those of Hiller, show that prolonged physical exercises facilitate the onset of sunstroke. It is therefore advisable in hot days to avoid as much as possible all causes of fatigue. As alcoholic intoxication predisposes to sunstroke, beverages containing alcohol must be avoided. Excesses in the use of animal foods and others, violent exercises, want of sleep, constipation, etc., should be avoided. Individuals suffering from malarial or other fevers, or from chronic liver or kidney diseases, run great risk in exposing themselves carelessly to the sun. Unnecessary exposure to the sun in summer is contraindicated.

X-RAYS

Pathological Effect.—The disturbances produced by x -rays are (1) local and (2) general.

1. **Local.**—**Dermatitis.**—The specific effect of the x -rays consists of eventual destruction of tissue (analogous to the ultraviolet rays of the spectrum when they are in superabundance). Ulcerations, necrosis, and sloughing of skin are frequent occurrences in exposures to x -rays. The consensus of opinion concerning x -ray burns is that the latter undergo three stages, namely: (1) hyperemia, leading to exfoliation in scales, degenerative changes with subsequent atrophy in the tissues depending upon the skin, as hair, nails, glands, etc.; (2) vesiculation; and (3) escharotic destruction; the intima of the bloodvessels becomes thickened and the whole process presents a chronic inflammation with all its usual consequences. The histological changes affect chiefly or exclusively the cellular elements of the skin, which undergo a slow degeneration with destruction, while the connective, the elastic, the muscular, and the cartilaginous tissues are not at all or only in a slight degree altered; or, if they do suffer, it is only secondarily to the inflammatory reactions. As to the cells themselves, the epithelial cells are affected first; and in

a slighter degree the cells of glandular organs and of vessels. The nucleus suffers conjointly with the cell-body. If the x -rays are intense, the leukocytes of the dilated vessels penetrate into the degenerated cells, and as phagocytes bring on their complete destruction and resorption. The cicatrization is of especial character; it is irregular, without a tendency to retraction, and perfectly white.

The x -ray burn has its *symptomatology*. At first there is a tingling sensation, which is followed by redness and swelling similar to the effect of solar rays. Later vesicles appear, which finally break down, leaving a raw surface. In severe cases ulceration will follow the vesiculation. As the process is inflammatory, a few general symptoms may be present: namely, chills, fever, pain, general malaise, etc. The characteristic feature of the lesions is their late appearance. The initial paresthetic disturbances may exist from a few days to two or three weeks before the erythema with the subsequent symptoms will be manifested. This is perhaps due to the cumulative property of x -rays. The healing process is also slow.

Atrophy of the Skin.—II. E. Schmidt, Kienbock, Gocht, Albers-Schönberg, Hahn, and Scholz, reported cases of marked atrophy of the skin with dystrophy or shedding of the nails, following x -ray exposure. They were probably due to angioneurotic and trophoneurotic processes.

(b) **Alopecia.**—In connection with this disturbance it is well to mention Gerwood's observation: in one case of his, curly hair grew in place of smooth; and in another black hair took the place of white.

(c) **Scleroderma-like** changes have been reported.

(d) **Gangrene** has been observed by some writers.

(e) **Cancer** was first reported by Allen and then by others.

(f) **Swelling of muscles** was observed by some French workers.

(g) **Lesions of the eye** leading almost to complete blindness. Cases of optic neuritis, ulceration of the cornea, conjunctivitis, myopia, amblyopia, and amaurosis are on record.

2. **General Symptoms.**—Oudin, Barthélemy, and Darier, who made extensive experimental studies and clinical observations, observed gastro-intestinal disorders from x -ray exposure, as, for example, symptoms of gastritis from exposure of the abdomen. Vertigo, nausea, headache, insomnia, rise of temperature, general nervousness, tremor, palpitation of the heart with oppression, and in some rare cases slight cerebral disturbances constituting the symptom-group of meningitis, were observed following x -ray treatment. A dermatitis may be accompanied in exceptional cases by a general illness. Holzknecht observed an intermittent vesperal fever (103° F. and above), chills, and concentrated urine. Fever usually lasts only a few days and ends with the beginning of a new skin. In four cases he observed skin lesions with a high temperature, which were taken for the eruption of scarlet fever. General toxemia has followed x -ray treatment of cancer and sarcoma; this is probably due to auto-intoxication produced by the cancerous and sarcomatous material. In exceptional cases, paralysis (mono- and paraplegia) and convulsions were observed. Finally, death followed in a few cases of x -ray exposure. In these cases this was secondary to a general septic

condition brought on by deep ulcerations with suppuration, but not by direct action of the rays; at least the histories of the cases are not convincing.

Effect of X-rays on Internal Organs.—Leukemia and diseases of the spleen have been favorably influenced by *x*-ray exposures. The investigations of Boermann and Linser have shown that *x*-rays first attack the bloodvessels and especially their intima; all other phenomena are secondary to this effect. Milchner and Mosse described changes in the bone-marrow. Symptoms of paralysis in small animals have also been noticed by some investigators, showing involvement of the nervous system. Whether in the latter case there were real pathological changes or only a dynamic disturbance, it is difficult to tell.

Albers-Schönberg¹ was the first to observe that *x*-rays produced sterility in rabbits and guinea-pigs without any change in the sexual potency. Death of spermatozoa was the immediate cause. Azoöspemia and atrophy of the testicles followed. The experiments consisted of daily exposures for fifteen to thirty minutes, and about one hundred and ninety-five to three hundred and seventy-seven minutes were necessary to produce the desired results. According to Friebe, the reason of the azoöspemia lies in the disappearance of the epithelium of the seminal canals, which leads to atrophy of the testicles. Seldin verified and corroborated in all its details the discovery of Albers-Schönberg and Friebe's explanation of the azoöspemia. Brown reported observations concerning the sexual condition of physicians and patients who have been exposed to the *x*-rays. "Men by their mere presence in an *x*-ray atmosphere incidental to radiography or the therapeutic uses of the rays, after a period of time as yet undetermined, will be rendered sterile. In the last few days ten individuals who have devoted more or less time to the work during the past three years—none of whom have had any venereal disease or traumatism involving the genitals—have been found to be the subjects of absolute azoöspemia. None of the number are conscious, however, of any change or deterioration in regard to their potency." In the report of Brown and Osgood² we find similar observations.

The action of Röntgen rays upon the female generative organs has also been the subject of special study. Ludwig Halberstaedter³ reported the results of his experiments on mammalia. Series of dogs were selected, and exposure to the rays was carried out in the usual manner. Ten or more days later extirpation of the ovaries was performed. Marked microscopic changes were noticed as to size of the organs and to the number of Graafian follicles. The later the examination was made the fewer follicles were found. This was verified by histological changes. In exposure to mild rays the disappearance of follicles is not as complete as in the experiments with stronger rays. Besides degeneration of the follicles, there are also a more or less large number of vacuolated spaces which are perhaps traces of degenerated follicles. The same experi-

¹ *Münch. med. Wochenschr.*, 1903, No. 43.

² *American Journal of Surgery*, April, 1905.

³ *Berl. klin. Wochenschr.*, January 16, 1905.

ments have also shown that ovaries present a far greater susceptibility to x -rays than the skin.

The practical importance of these investigations is too evident to dwell upon. Prophylaxis in an x -ray atmosphere is of paramount importance; adequate protection to all parts of the body not directly exposed for examination or treatment should be provided. On the other hand, the facts herein set forth give us a convenient, painless, and harmless method for rendering a male or female sterile in cases in which sterility must be obtained for serious reasons. Resection of seminal ducts, and removal of ovaries, although more or less safe with the modern surgical methods, are nevertheless inferior to bloodless methods.

Pathogenesis.—It is yet debatable what particular element plays such an important rôle in producing lesions during exposure to x -rays. Some believe that it is the ozone which is formed around the tube; others, electric discharges emanating from the tubes; and still others, the x -rays themselves. The last view is accepted by the majority of writers. It is their direct action that causes the lesions. According to Scholz, the x -rays have a specific action on the elements of the skin, causing a slow degeneration of the cells of epidermis, hair follicles, glands, and also of the connective-tissue cells of the corium; the nucleus is affected by the degenerative process as well as the protoplasm of the cell. As to the question whether the x -rays have only a local or a general effect on all the tissues through which they pass, the consensus of opinion is that the first effect is on the skin; the deeper tissues, as muscles and bones, are influenced only slightly. If necrosis follows, it is only secondary to a pronounced inflammation and ulceration. Curiously enough, they affect not only the skin at the point of their penetration, but also at the level of their exit. Revillet and Kummel have shown that illumination of the thorax produced an erythema on the thorax and back. As to the intermediate organs the effect is usually little or none whatever.

Treatment.—There is no special treatment for x -ray accidents. As the superficial lesions are similar to those produced by the violet rays of the spectrum, Bar's suggestion as to the use of red light, which is proved to be antagonistic to the violet, is certainly very interesting. He at least obtained very encouraging results. On the other hand, Kaiser reported recently that blue light rays gave him good results. Pain may be relieved by static electricity, according to d'Apostoli. High-frequency currents have been also suggested for x -ray burns. As to local applications to the diseased tissues, various drugs have been recommended, but none has any specific value. Nitrate of silver (2 per cent.), picric acid ($\frac{1}{2}$ per cent.), zinc ointment, cocaine (for pain), peroxide (in cases of exudation and suppuration), and others are remedies advised in x -ray burns; but they have been used in burns of any other origin. It is well, however, to remember that the effect of the drugs just mentioned is not as prompt as in ordinary burns.

A few hints concerning special features of the action of x -rays will aid in forming an idea of prophylactic measures. Daily radiation has a cumulative effect. Various parts of the body are differently affected. Parts covered with hair (head and chin), the nails, and bloodvessels,

are more predisposed to inflammatory dermatitis than any other portion. A diseased skin is much more easily penetrated by x -rays than a healthy skin. According to Scholz the more rays that emanate from the tube the stronger is the effect on the skin. He also advises the use of soft tubes for therapeutic purposes instead of hard ones, as from the latter emanate few x -rays, but there is much electrical discharge. Large doses, prolonged exposures, and proximity of the tube are capable of devitalizing tissue-elements and causing their degeneration. An important point to remember concerning the administration of x -rays is the danger of disseminating a malignant process or of causing a more rapid growth.

OTHER RAYS

Becquerel's discovery of rays given off by uranium (pitchblende) or its salts led to the discovery of radium and polonium by M. and Mme. Curie; also of actinium (Debienne), of rays N and N' (Blondlot and Charpentier). They all possess a highly penetrating power which is not present in ordinary light. Although the therapeutic value of these rays is at present not definitely determined, we know, nevertheless, that some beneficial effects are established. Very mild applications modify the nutrition of tissues and stimulate the functions of glands. Epithelioma, lupus, and keloids are favorably influenced. In tuberculous conditions of the air-passages inhalations of air laden with radium emanations have proved to be beneficial. Damages are sometimes produced by their indiscriminate use. Welkhoff and Giesel have first shown the deleterious effect of Becquerel's rays upon the skin: namely, ulcerations and necrosis. Similarly to x -rays there is a latent period only after which the lesions begin to appear; the redness appears only a few days after the exposure, the ulceration weeks later. In Curie's case of his own person ulceration appeared fifty-two days after the onset. V. Henri and A. Mayer have demonstrated the effect of radium on the blood; hemoglobin is transformed into methemoglobin, and its solubility is diminished. Askinass and Caspari have shown that Becquerel's and Curie's rays have an inhibitory influence upon the metabolism in living tissue. In this respect their effect is identical with that of x -rays, but their action is more intense and destructive than the latter. Alquier and Faure-Bealien¹ have shown that radium applied to the cranium or to the spine in therapeutic doses may produce minute hemorrhages without discoverable alterations in the nervous tissue. The hemorrhages are identical with those found in the brain or on its surface in patients who died from epilepsy.

ELECTRICITY²

Electricity may under certain conditions produce local and general disturbances and even death. The universal utilization of electrical

¹ *Now. Iconogr. d. la Salpêtrière*, 1909.

² An excellent summary of the effects of Electric Currents and Lightning is given in the Goulstonian Lectures for 1913 by A. J. Jex-Blake, *British Medical Journal*, 1913, i, 425, 548, and 601.

energy in industry exposes human beings to its deleterious effects to a considerable degree. The accidents caused by electrical currents, and the facility with which they are produced, make it the duty of physicians to become familiar with these accidents and with the means of removing the consequences. The currents become dangerous only when their energy reached the high degree necessary for industry. Everybody is exposed to the danger of receiving accidental electrical discharges more or less powerful.

It is considered that contact with a wire in which circulates electricity of 500 volts is fatal. Resistance of the human body to the passage of a current of this intensity is considerable. It varies with the degree, extent, and duration of contact, the state of moisture and thickness of the skin, the state of general health, and whether alcoholism is present or not. The immediate effect of electrical current may be death, shock with temporary loss of consciousness, painful sensations, and, finally, burns of the skin.

Death.—When an individual is stricken by a fatal current there is a violent tetanic contraction of all the muscles of the body, followed by loss of consciousness. Three or four minutes later the respiration ceases. The mechanism of death, according to Provost and Battelli, depends upon the degree of tension of the current. In high tension (1200 volts or above) there is inhibition of the nervous centres; the respiratory centre is first affected, and the heart ceases to beat only subsequently to asphyxia.

Low-tension currents (not above 120 volts) produce paralysis of the heart, but the respiration continues for a certain time. The heart shows a fibrillary tremor, and as soon as the latter appears the beating is immediately arrested and no more blood is thrown into the circulation. Currents of average tension (240 to 600 volts) produce paralysis of the heart in a state of fibrillary tremor, and an absolute cessation of respiration. We therefore see that the fibrillary tremor of the heart is the most dreaded phenomenon, while the shock of the nervous centres is of no special import. The cessation of the heart-beat is independent of the extrinsic innervation of its muscles. When there is no fibrillary contraction of the heart, there is no danger to life.

The currents used in industry are either continuous or alternating. The continuous current requires a higher voltage than the alternating current to bring on a paralysis of the heart. On the other hand, the inhibition of the nervous system is more pronounced with continuous than with alternating currents.

Other Consequences.—If death does not ensue in ordinary conditions the sudden contact with an electrical conductor will produce syncope, which is usually of short duration. The reëstablishment of normal functions may be complete and rapid, but sometimes the various nervous disturbances may remain very tenaciously. In the latter case there is usually a state of hebetude for several days, accompanied by weakness, headache, and sometimes palpitation of the heart. In some cases there was a state of mental confusion or delirium, tremor, and a general depression of the nervous system similar to that following traumatism.

Psychoses have been observed but the mental disturbances were transient. Amnesia was reported by Heusner, Ebertz, Winiwarter, and others. Painful sensations in the muscles and in the thorax have been recorded as of frequent occurrence.

Besides these immediate disturbances, there are quite a number resembling well-defined nervous affections. Functional nervous diseases, as hysteria and neurasthenia, are common occurrences after an electrical shock. Abundant examples of either of these two neuroses, or of a combination of both, are found in recent literature. One of the most typical cases of hysteria was observed by the writer in a woman who was touched at the elbow by an electric wire which broke while she was walking on the street. A complete hemianesthesia to touch, pain, and temperature, covering also the face, pharynx, conjunctiva, ear, and head, was present in this case; the visual field was markedly contracted on the same side. The sensory disturbances persisted in spite of complete recovery from the immediate effects of the electric shock. Another young woman was struck by lightning while sitting near an open window. She was seen by the writer after she regained consciousness, viz., about an hour after the shock. She developed typical hysterical paroxysms; suddenly she would fall, being seized with a slight tremor in the extremities; a minute later the trunk would begin to assume various positions, opisthotonos being the most frequent. At the same time the patient would scream, or laugh loudly, or cry. The seizure would last ten minutes. At first the attacks were very frequent, averaging five or six a day. A month later they began to disappear gradually, and at the end of three months she was free from them.

Epileptiform and apoplectiform seizures are reported. Batteli¹ made a special study of the continuous and alternating industrial currents with a comparatively low voltage (120 to 240 volts). He observed that when one electrode is placed in the mouth or nostrils and the other on the neck, the heart is not affected, the nervous centres alone being excited. With this arrangement an epileptiform convulsion makes its immediate appearance as soon as the current is closed. A contact of $\frac{1}{20}$ of a second is sufficient to bring on an attack; the latter becomes very violent if the duration of the contact is prolonged to $\frac{1}{10}$ or $\frac{1}{5}$ of a second. The attacks present the typical tonic and clonic contractions of the muscles, with froth at the mouth and dilated pupils, followed by a comatose state. Bulbar symptoms, transient in character, were reported in a few cases, but in view of their temporary nature they were probably cases of functional neuroses. However, Charles K. Mills reported two cases observed by him personally in which there cannot be any doubt of the organic character of the involvement of the medulla.

There are also in the literature records of apparently undoubted cases of hemiplegia, spastic paraplegia, and of disseminated sclerosis, following lightning or shocks from other electric sources, but these records are clinical. The pathological findings of those few cases that come to autopsy are in general negative, except a few capillary hemor-

¹ Société de Biologie, 1903.

rhages or small cellular changes in some cases. Congestion of the brain and cord was found in some cases (Kratter).

Eye disturbances have been observed by various authors. Dimness of vision, ptosis, contraction of pupils, sluggish reflex reactions, sub-conjunctival ecchymoses, cloudiness of cornea—these are the external ocular changes reported. In a certain number of cases profound alterations of the eye were noticed, viz., hemorrhages in the retina, with pigmentation, tearing, bleeding, and rupture of the choroid, iridocyclitis, luxation of the retina, anemia of the optic nerve, optic atrophy, and blindness. There are reports of the formation of cataract. Hess observed, experimentally, cataract formation in animals. Disturbances of the auditory apparatus occurred in many cases. Pain in the ear, with difficulty of hearing, is a frequent symptom following electric shock. The writer recalls a case of absolute deafness in a man of twenty-five occurring after having been shocked by lightning. In this case there was loss of consciousness and a partial hemiplegia on the left side; but the deafness was complete in both ears. Only one month later improvement in hearing appeared. The patient recovered entirely. Kayser and Freund report permanent deafness from paralysis of the eighth nerve, with or without simultaneous perforation of the drum.

Burns.—A conductor charged with electricity will produce burns in living tissue when it is brought in contact with the latter. Radiation of electric light may produce some superficial burns, but the appearance of the burns and the accompanying general symptoms are different when electricity has a direct effect on tissue from immediate contact. The effect of a current is not always in direct relation with its strength, as sometimes currents of 5000 volts produce only superficial burns, and of 500 volts deep burns. Individual circumstances accompanying the accident—duration and degree of contact, dampness of skin, the degree of cleanliness of the latter—all are of great importance as to the effect of the contact.

In electrical burns all the tissues, from the epidermis to the bones, may be affected. They may be superficial or deep. They are usually not limited to the dermis; the muscle and bones are also affected. The loss of substance may be small, or may invade a portion of the limb. Immediately after the contact the skin becomes black, and the affected portion is soon covered with a hard layer resembling parchment. During the process of reparation the wound acquires a red and smooth surface. There is never present at the periphery that whitish ring which is found in ordinary burns. Electrical wounds never suppurate and are never moist; the parchment-like layer is preserved until a new epidermis is formed. The characteristic feature of electrical burns consists in their absolute painlessness during the entire process of healing. The duration depends upon the degree of the burns; so that, when the bone is involved, the course will be prolonged and complications will set in. Superficial burns heal up entirely and rapidly. In deep burns gangrene may occur and necessitate amputation of the limb.

Burns may be accompanied by a nervous shock more or less serious, frequently by syncope. The latter may be fatal and the patient dies

in a few minutes despite all possible care. We said above that from a tension of 500 to 600 volts upward, electrical accidents may be fatal. It is to be noted that the voltage alone does not determine the question of death. Perhaps the danger lies in the fact that an electrical burn forms a bad contact by interposition of gaseous products between the tissue and the metallic conductor. The histological changes of electrical burns are identical with those of *x-ray* burns.

Treatment of Accidents Produced by Electricity.—When the person is still in contact with the conductor, an effort should be made to form a short circuit, by means of a body which is considered a good insulator, as a piece of wood. If there is no object at hand, we should free the victim by giving him a push with the foot; the person that touches the victim will feel but a slight shock, because the resistance of the shoes is great. After the contact is interrupted, recovery usually follows if there is no loss of consciousness. If consciousness is lost respiration may continue or else be arrested. In the first case the ordinary means usually employed in syncope should be applied, as traction of the tongue, friction, cold water, etc. In the second case it is advisable to institute artificial respiration at once, if the heart continues to beat. In case the heart is in a state of fibrillary tremor, artificial respiration is useless.

Burns should be treated on general principles. The affected limb should be immobilized; protection of the wound with sterilized gauze is usually sufficient. In cases of extensive burns, skin grafting is indicated.

AIR

Pathological Effect.—Carbon dioxide is an abnoxious element, and may become dangerous if present in excess. In poorly ventilated rooms one feels uncomfortable, and may have a sense of weight, uneasiness, or pain in the head, dizziness, or ringing in the ears; sometimes vomiting, disposition to sleep, difficult respiration, rapid loss of sensibility; and at times syncope. The discomfort is not due to carbon dioxide, as a rule, but to lack of movement of the air and the amount of humidity.

The action of humidity is very important from the standpoint of respiration and the function of the skin. In dry and warm air the cutaneous evaporation is very active; in dry and cold air the pulmonary evaporation is stimulated. Humid and cold air diminishes the cutaneous evaporation, and when perspiration is not evaporated the variations in the temperature are apt to cause diseases which are usually attributed to cold. Besides, the appetite and metabolism in general suffer and disable the affected individuals for any work; intestinal diseases develop easily, and pulmonary tuberculosis finds a favorable condition for its rapid development. Moist and warm air has a special affinity for organic matter, and therefore predisposes to development of pathogenic organisms.

The disturbance in the proportion of the normal constituent elements of air is observed not only in association with organic material subject to putrefaction, but also in changes of *atmospheric pressure*. In normal conditions there is an antagonism between the internal pressure and

the pressure produced by the surrounding atmosphere. Equilibrium is maintained when one counteracts the other; but should local atmospheric disturbances make their appearances, air pressure is felt.

Oxygen is indispensable for life, and the purity of air is judged by the presence of a sufficient amount of this gas. If oxygen is conducive to health, it may under certain conditions become obnoxious and cause a pathological state. The latter is precisely observed in changes of atmospheric pressure. Paul Bert says pure oxygen may act as a poison, and animals die in ordinary air when pressure of O falls to 3.4 per cent. of atmosphere, while in superoxygenated air they die when pressure of CO₂ rises to 25 per cent. of atmosphere. In collecting facts regarding the effect of various degrees of air pressure on human life, the method of balloon-travel have been employed to learn the effect of rarefied air on the human organism. The effects of mountain climbing have also been studied. Alterations of atmospheric pressure have been regarded by some as coincident with pulmonary congestion and with neuralgic and rheumatic pains; but a well-defined symptom-group due exclusively and directly to altered air pressure we find in (a) *mal des montagnes* and (b) *caisson disease*.

Mountain Sickness (*Mal des Montagnes*).—At the height of 3000 to 4500 meters the first noticeable symptoms are palpitation of the heart and rapid pulse. Soon the respiration becomes accelerated; the patient becomes restless, cannot sleep, and sometimes has vomiting spells. There is more or less pronounced pain in the knees and legs. Walking is difficult, and the patient feels exhausted. At the same time thirst increases the suffering. The tongue is dry; the appetite is lost; nausea and eructations torture the patient. In extreme cases hemorrhages may occur which are followed by syncopal attacks. The hemorrhages are most frequently from the mucous membranes of the air passages. Lazarus also observed cyanosis of the extremities when a height of 7000 meters is reached. The symptoms are analogous to those of ascent in a balloon, but it is remarkable that in the latter case the effects of diminished pressure are not felt until twice the height has been reached. The reason of it lies in the muscular energy consumed in climbing. This is accompanied by a larger loss of calories than the organism can supply, as the respiratory combustion cannot furnish a sufficient amount of heat because of low density of the air. The body temperature falls below normal and the ascent becomes difficult. Consequently in *mal des montagnes* we have two factors: the effects of rarefaction of air and those of fatigue.

The effects of *mal des montagnes* are not uniform in various individuals and at various heights. They depend upon the age, habits, antecedent health, etc. At 3000 meters the symptom-group is present in every case. Passive movements can be produced in healthy individuals without marked effect in their health even at the level of 4000 meters. Active movements even at a lower height will produce the symptoms enumerated above. This observation is a sufficient hint for preventive measures. In addition to the latter, care should also be taken not to remain in the rarefied air longer than two or three hours.

When a more or less prolonged sojourn in mountainous regions is taken up by persons who come from lower altitudes, they become subject to the following symptoms, which are particularly marked when the barometer stands low: hemorrhages and bronchial and nasal catarrhs. Attacks of hemoptysis are often seen in tuberculous patients who come to high altitudes. Epistaxis is observed in perfectly healthy individuals. The catarrhal trouble is quite frequent and rebellious to treatment. W. H. Gardner described a curious symptom-group observed on himself. Besides the usual symptoms described above, he developed a confusion of ideas and a paretic condition on the entire left side of the body, including the tongue, so that he could not articulate; he also felt a throbbing in the carotids, and his pupils were dilated. He describes several cases, in one of which he also observed hemianesthesia followed by epileptiform convulsions on the same side; in other cases he observed apoplectic attacks with or without aphasia.

Pathology.—As to the pathogenesis of the affection, several theories have been advanced. Some believe that, in view of the fact that the symptoms are analogous to the physiological and pathological effects of ozone, and that ozone is more abundant the higher the level of atmospheric air is considered, for these reasons it is probably the direct cause of mal des montagnes. Others believe that the lowering of air pressure produces a congestion of inner organs, or circulatory disturbances. Paul Bert has shown that the cause of the disturbances lies in the diminution of oxygen in the inhaled air, and that the symptoms can be entirely removed by inhalations of oxygen. The latter view is the most accepted, as the majority of the symptoms can be readily explained. In fact, the accelerated respiratory and circulatory movements have for their purpose not only a larger absorption of oxygen, but also the removal of carbon dioxide. But the exhalation, although very active, is not longer sufficient for maintaining the normal composition of the blood, which is saturated with CO_2 . In this fact lies the reason of the headache, the nausea, the irresistible insomnia, the low bodily temperature, and other symptoms observed in travellers on mountains. The treatment, therefore, consists of supplying the gas which is wanting.

Caisson Disease, or Diver's Paralysis.—Above, we considered the effect of rarefied air on human economy. If the condition is reversed—viz., if the organism is subjected to a high atmospheric pressure—the morbid manifestations will be almost exclusively confined to the nervous system. The symptoms observed in divers or workers in caissons appear only after they return to the surface. It is therefore the lessened atmospheric pressure which is the immediate cause of the disorder of the nervous system. Nevertheless, as this lessening follows the increased pressure beneath the surface, it is the latter that is primarily at fault.

Pathogenesis and Pathology.—There are only two theories in vogue. According to one of them, the so-called gaseous theory, the blood while under high pressure becomes overcharged with gas (oxygen and carbonic acid), and the longer the exposure the greater the amount of gas. When the surface is reached, the gas attempts to escape through the lungs, but this can be done only gradually and progressively. In the meantime

the superfluous gas circulates in the blood in bubbles, and may either form emboli or escape through the vessel walls into the surrounding tissues and consequently produce considerable pressure. If during this time the lungs continue to remove gradually some superfluous gas, the air of the tissues may be gradually reabsorbed and thus relieve the pressure. This is precisely what is observed in the majority of cases; at first paralysis with the associated symptoms, and then their gradual disappearance. The reason of the special effect of this mechanism on the nervous system lies in the fact that the latter (brain and cord) are situated in cavities which to a large degree are hermetically closed. The spinal cord suffers the most, as, besides the cause just mentioned, its return circulation is very slow because of the large number of plexuses. There are a number of facts, particularly experimental, which are in accord with this theory.

According to the other view there is a congestion followed by a stasis. The high pressure drives the blood from the periphery to the internal organs, especially to the nervous system. The bloodvessels of the latter, unlike those of other organs, have no support from counter-pressure, and therefore remain dilated. A paralysis of the vessel walls follows. When the atmospheric pressure is diminished, and consequently the blood-pressure relieved, the paralyzed vessels cannot follow, and stasis of the brain and cord will be the result.

While both theories are tenable and apparently do explain all the symptoms of the affection, it is nevertheless difficult as yet to tell which of the two has the more solid basis. The most constant microscopic changes found in almost every case are congestion of brain and cord and internal organs in acute cases, and softening in chronic cases. In the incurable cases of long standing in which the condition remained permanent until death, lesions of typical chronic myelitis were the usual findings.

Symptoms.—Shortly after the return to the surface and after a prodromal stage consisting of pain, more or less severe, in the large joints, and also in the epigastrium and sometimes over the entire body, a paralysis occurs. The most frequent form of this is paraplegia, but sometimes hemiplegia is observed. The onset and the character of the paralysis is very similar to that of transverse myelitis. If we take into consideration the frequent involvement of the sphincters (retention and constipation), and the sensory disturbances, the resemblance to myelitis will be complete. All these symptoms may present variations in degree; in some cases the loss of power is only partial, in others more or less pronounced, and in still others absolute. Also both extremities may not equally be involved in regard to motor power as well as to sensations. In some cases, in addition to the myelitic symptoms, there are also vertigo, headache, vomiting, slight confusion, convulsions, and double vision. Prostration is present in more severe cases. In fatal cases, deep coma, irregular respiration, and symptoms of cardiac paralysis announce approaching death. As an occasional occurrence we may mention small perforations of the ear-drums, which are due to the pressure either externally or from within outward.

Prognosis.—Generally speaking, recovery occurs frequently. In complete paralysis the loss of power may last only a few days. In severe cases the power may never return and the victim will remain permanently crippled.¹ Death in protracted cases results from the same causes as in chronic myelitis: namely, from suppurating bed-sores, cystitis, pyelitis, etc., or from an intercurrent disease. On the other hand, death may occur shortly after the onset, as in acute myelitis. It usually occurs in cases that are grave from the first. The hemiplegic form of paralysis bears usually a favorable prognosis. Deep coma with irregular respiration is usually a bad omen.

The degree of damage and consequently the probabilities of recovery depend in a general way largely upon personal predisposition, previous health (condition of heart, bloodvessels, kidneys, etc.), habits (alcoholism), age (fifty years is considered the maximum), upon the length of time spent in the caisson under high pressure, and finally and mainly upon the manner in which the diver is brought to the surface. That is to say, the less rapid and abrupt the decompression of air is done, the less damage the nervous system undergoes and the more chances for recovery there are.

Treatment.—The management of well-developed symptoms of myelitis indicating a permanent and definite lesion of the cord, must be conducted on the same principles as in myelitis. When the symptoms are only commencing to appear, it has been found that with an immediate return to the surface, or by subjecting the individual to increased atmospheric pressure in any manner at all (pneumatic cabinet, etc.), the symptoms may disappear. It is an absolute necessity to have on hand an apparatus in which the patient could undergo high-pressure séances.

Preventive measures constitute the most important part of the treatment. Bad physical health, diseases of the kidneys or heart, alcoholism, obesity, and, finally, hunger are all contra-indications for subjecting one's self to the high atmospheric pressure. As to the limit of time which is permissible to spend in the caisson, Collingswood's rule is particularly to be recommended. For the first exposure only one hour; for those who are accustomed to the work the number of hours should decrease as the number of atmospheres increases, as, for example, three hours in four atmospheres, four hours in three atmospheres, etc. The locks with which the caissons are supplied, and in which the pressure is gradually reduced, should be used very frequently, according to Smith. Haldane and Boycott² have worked out for the English Admiralty divers rules for a system of gradual decompression. If a diver has been working at a depth of 144 feet for ninety minutes, he then is raised to 55 feet; after a rest of ten minutes he goes up to 40 feet; again after a rest of ten minutes, he goes up to 30 feet and waits twenty minutes; he goes up 20 feet and waits thirty minutes; goes up to 10 feet, waits thirty-five minutes, and then leaves the water.³

¹ See Bassoe, *Amer. Jour. Med. Sc.*, 1913, cxlv, 526.

² *Journal of Hygiene*, Cambridge, 1908, viii, 342.

³ See Report of the Commission on Occupational Diseases of Illinois, Chicago, 1911.

HEAT AND COLD

Heat.—The effect of heat must be considered from three standpoints: (1) Immediate contact of living tissue with a hot object; (2) effect of solar heat (see Sunstroke and Sun-traumatism); (3) effect of hot climates; and (4) a special effect on muscles, producing myospasm.

Solid or liquid objects, and gas and vapors, when their temperatures are elevated, will produce burns on coming in contact with living tissue; local destruction of skin and mucous membranes will be the consequence.

Fluids, when they do not reach a temperature of 100° , produce only a slight erythema. Water boils at the temperature of 100° C.; salty water and oil must have a larger quantity of calories and are therefore to be feared. Burns of mucous membranes of the rectum and vagina occur when very hot enemas or injections are administered. Oedema of the glottis may be the consequence of burns of buccal, pharyngeal, and oesophageal mucous membranes. Caustic fluids taken by mistake or in attempting suicide lead to very grave injuries of the mucous membranes. *Solid* objects, especially metals at a red heat, produce deep lesions; but the burn is confined to the point of application if the substance is not adherent. *Gas* causes accidents through its flame. Those whose work exposes them to explosions (chemists, miners, etc.) are frequently victims of burns; their clothing takes fire and cannot be separated from the body; the skin becomes carbonized and the subcutaneous fat burns; the consequences may be very serious. *Hot vapors* are particularly obnoxious. Droplets of hot water accumulated on the skin will burn it, but they may be also inhaled and penetrate the mucous membranes of the larynx and lungs.

In *burns* we meet with all degrees of active hyperemia and formation of oedema, hemorrhages, and necrosis in the skin. Since Dupuytren, it has been generally accepted to consider six degrees of burns. The *first* degree is characterized by *redness, pain, and tumefaction*. The pain is pronounced at the beginning. The swelling is of short duration. The symptoms are transient, and desquamation of the epithelium takes place. In the *second* degree the Malpighian layer is affected. The epidermis is elevated by vesicles. When the latter are ruptured and the epidermis is removed, granulation and suppuration are found on the underlying layer, which is extremely painful. Deformed scars will always form, if the epidermis is removed. It is therefore advisable to leave the epidermis in place. The *third* degree is characterized by destruction of all the superficial layers of the dermis. The vesicles, which are large, do not contain a serous fluid as in the preceding degree, but a dark, bloody fluid. Sometimes dry, dark, or yellow scabs are formed. The pain is exquisite, especially on the sixth or seventh day, when the scab falls off. The latter leaves a granulated and suppurating surface which is replaced later by a deformed cicatrix. In the *fourth* degree the destruction of the skin is complete; even the subcutaneous cellular tissue is affected. The scabs are here more or less large, dark, and dry. Pain is not pronounced, because the nerve ends are destroyed. The gangrenous layers fall off and cause sometimes an inflammatory con-

dition. The cicatrices are formed very slowly and are very irregular. In the *fifth* degree we often find destruction of skin, muscles, bloodvessels, and nerve trunks. When the scabs fall off, sometimes articular cavities are laid open. When the gangrenous tissue falls off, purulent arthritis, visceral inflammation, and abundant hemorrhages may occur. In the *sixth* degree all the tissues are carbonized, the periosteum is destroyed, the bone is necrosed, and an entire limb may be lost.

In addition to local symptoms there are frequently general phenomena which depend upon the extent of the lesion. When the burn is grave, the pain may be so intolerable that the patient falls in a stuporous state. He is somnolent, does not speak or move; the face is pale; the skin is covered with a cold perspiration; the temperature goes down below normal; the pulse is imperceptible; and the respiration becomes irregular; anuria may occur. In another series of cases with the same lesions the general condition is of a diametrically opposite character; extreme excitement with delirium and convulsions will be observed. In a certain number of cases there is a marked elevation of temperature, which is due to visceral inflammation. Here we observe loss of appetite; constipation, or else a diarrhœa; generalized bronchitis, bronchopneumonia, or pleurisy. The kidneys may become involved, and albumin is found in the urine. Finally, cerebral congestion, with exudation in the ventricles, has also been observed.

During the period of disappearance of the scabs the suppuration described above is always accompanied by general symptoms. In pronounced cases amyloid degeneration of the viscera may occur and lead to cachexia and death. In other cases new infections may occur in the suppurating wound: erysipelas, septicemia, secondary hemorrhages, and tetanus may develop.

Pathology and Pathogenesis.—The common findings are congestion of the digestive and respiratory tracts and of the nervous system. But the complications cited above will add other lesions independently of burns. As to the pathogenesis of burns, various views have been advanced, and among them the ideas of Metchnikoff's and Ehrlich's schools are the most acceptable. In burns there is complete or partial destruction of the cell elements of the blood; this has for consequence formation and absorption of cell poison (hematoxin). In extensive burns we have to deal with destruction of a greater number of cells, and therefore with a larger surface for absorption of the products of this destruction. Capillary emboli, thrombi, and infarcts, especially in the kidneys, are of frequent occurrence; they explain the cases of sudden death so frequent after extensive burns.

Prognosis.—This depends largely on the extent and depth of the burn and upon the importance of the affected organs. A lesion which would be insignificant on the skin will be of paramount gravity if it occurs in the throat, as œdema of the glottis may ensue and be followed by death. On the other hand, a burn of second degree, if it is extensive, may be more serious than one of the third or fourth degree which is less extensive. The complications play a great rôle in the course and termination of a burn.

Treatment.—In burns of the first degree, sedatives for the pain and external applications of liniments containing cocaine or morphine are sometimes sufficient. Prolonged baths at a temperature slightly lower than the body temperature are particularly recommended. In burns of the second degree one must not remove the epidermis raised by the vesicles. The latter should be punctured at its lowest point. If, however, the epidermis is accidentally removed, the burn should be covered with a thick layer of antiseptic cotton. Cotton is a good filter for air, protects the nerve ends, and lessens the inflammatory condition by pressure. In case the cotton is moist with exudation from the wound, it must be changed. It should remain in place until a new epidermis is formed. When the burns are deep and scabs are formed, care should be taken to avoid formations of irregular cicatrices. Antiseptic dressings, and particularly carbolyzed vaseline, or iodoform incorporated in vaseline, and also gauze saturated with a weak solution of sublimate and protected with oiled silk, are all of value; they prevent extensive suppuration with its usual complications. In some cases it is extremely difficult if not impossible to avoid deformed cicatrices; deformities about the mouth, eyelids, and nostrils have been reported. Syndactylism occurs in cases in which the nude surface of one finger is in contact with the next finger. Similar adhesions have been observed between the arm and thorax. In such cases skin grafting will be of great service. In extreme cases, when the destruction of the skin or of a portion of a limb is so great that the function will be hopelessly disturbed, amputation becomes necessary.

As to the general symptoms accompanying burns, they must be treated on general principles. For depression, use stimulants; for excitement and pain, sedatives. Good, nutritious food should always be given.

Hot Climates and Health.—A question of great practical importance is the morbid effect of hot climates on health. If an individual from a moderate climate is thrown accidentally or otherwise into an atmosphere with an elevated temperature, what will be the effect on his health? The first symptom noticeable will be increase of perspiration. This is followed by a low arterial tension. The urine is reduced. While the lungs expand, the number of inspirations is reduced, and as hot air contains less oxygen than cold, the general metabolism is diminished. The tolerability or intolerability of hot air is always associated with humidity. Atmospheric humidity interferes with free evaporation of sweat, and this necessarily interferes with the mechanism concerned in heat generation. A diminution of capacity for intellectual work—with a condition of languor and general weakness, loss of appetite, disturbance of digestion, of respiration, and of circulation, are the usual symptoms observed in individuals who come from a moderate climate to reside a more or less prolonged period of time in tropical countries.

Hot air with moisture predisposes to various affections, as intestinal diseases and bronchitis. The latest reports on mortality in tropical climates show that there is a special group of diseases which predominate and are highly fatal. They are nervous diseases, and convulsions in children.

Myospasm Caused by Exposure to Heat.—In 1904 and in 1908¹ Edsall described the following manifestations occurring after exposure to heat. The patient is suddenly seized with an exceedingly painful tonic spasm lasting a half a minute or a minute. The muscles involved are those of the forearms, legs, and abdomen. Between the attacks fibrillary contractions of the affected muscles are continuously present. The spasmodic muscular contractions resemble tetany, except for the absence of Chvostek's, Trousseau's, and Hoffmann's phenomena. The affected muscles are easily stimulated: the least voluntary act or a slight palpation brings on a spasm. The spontaneous spasms last but twenty-four hours, after which exhaustion is noticeable. No other abnormal phenomenon is observed in connection with the myospasm. There are no objective sensory disturbances, no involvement of the sphincters, and the cutaneous and deep reflexes are not altered. The temperature is normal. The pulse is somewhat accelerated.

The affection occurs in men employed in iron works or in firerooms of vessels where they are exposed to intense heat. Cameron, who had the opportunity to see a large number of such cases, says that the condition had been known long before Edsall's observation under the name of "Mill Cramp." He observed that overexertion predisposes to the spasm and one attack predisposes to others. The pathogenesis of the disease is probably a degenerative state of the muscles. The treatment consists first of all of removal from exposure to heat, but symptomatically only sedatives or anesthetics may be thought of. Cameron obtained satisfactory results in some cases from applications of a mild interrupted current. The prognosis, as a rule, is good. The recovery may be rapid and complete, without serious consequences. However, some fatal cases have been reported and death is probably due to a spasm of the heart muscle.

Cold.—The effect varies with the age, with the state of general health, with constitutional diseases, fatigue, alcoholism, and, finally, upon the degree of cold. We will consider first the local effect of cold and then its general effect.

The effect of extreme cold upon the portions of the body which are exposed (feet, hands, ear, nose) presents three degrees. In the first degree there is a dark redness of the skin. The circulation is poor, the stagnation of the blood in the peripheral capillaries leads to infiltration of the subcutaneous tissue, and the skin is thickened. When the skin is exposed to heat, tingling and itching will be present. Generally the condition does not last long. In some cases it may become chronic. The second degree is characterized by ulcerations. In acute forms they appear at once. The epidermis is raised by a serous or bloody fluid; the thin membrane becomes detached, and an ulcerated surface is seen. In the chronic form the skin, which is infiltrated, bursts, and the yellow-brownish fluid turns into crusts, under which pus is accumulated. The third degree is characterized by death of the dermis and sometimes of

¹ *Amer. Jour. Med. Sc.*, 1904, cxxviii, 1003, and *Jour. Am. Med. Assn.*, 1908, li, 1969.

the other underlying tissues. Elimination of necrosed tissue begins very soon. If it is moderate, the sloughing will leave a bleeding, ulcerated surface, under which is sometimes found diseased bone.

Pathology and Pathogenesis.—Laveran and Cohnheim have studied the effect of cold, and found the bloodvessels to be the main tissue involved. The action of cold consists in narrowing the lumen of the bloodvessels, which may go even to its complete obliteration; the blood does not circulate and the involved area becomes white. Soon the capillaries dilate so that the circulation is slow and sometimes arrested. Thrombosis is the usual consequence, and small emboli may be detached and thrown into the general circulation. Changes in nerves are sometimes very pronounced; ruptures of the vasa nervorum and interstitial hemorrhages have been observed. Laveran and Tillaux speak of fatty degeneration of the myelin sheath, a fact which will explain muscular atrophy, pain, and trophic ulcers, with anesthesia of the skin. The inflammation of the neuritis may sometimes ascend to the cord. Other lesions were observed. Mathieu and Gubler speak of visceral congestion caused by capillary emboli; Laveran, of loss of mobility of leukocytes.

Prognosis.—The first and second degrees may run their course without general disturbances. However, in soldiers who suffer hardships, in aged people and cachectic individuals, oedema of the face and of eyelids, and albuminuria were observed. Weak individuals, old people, children, those who overfatigue themselves, those who do not eat enough, those who use alcohol to excess, are all very readily predisposed to the effects of cold, and in such cases the prognosis is therefore always serious. During the stage of suppuration general septicemia may occur. Recovery is usually slow; the cicatrization is very sluggish, and may be arrested from the slightest cause. This is particularly true in regard to individuals of lymphatic nature.

Treatment.—Prophylactic measures are of utmost importance. The extremities (hands and feet) should be well protected. Sudden changes of temperature should be avoided. Dry astringent friction and massage are recommended.

When the first degree is present, the congestion of the skin will be relieved by washing it with a stimulating fluid (alcohol and others). When ulcerations make their appearance, they should be protected from infection. The third degree requires special attention. The greatest precaution is necessary to avoid extension of the inflammation. The well-known friction of frozen limbs with snow or with very cold water is not to be neglected. In case of apparent death, artificial respiration is indicated. There are cases on record showing that individuals after having remained under snow for several days could be brought to life with artificial respiration. It is therefore important to have recourse to it in every case.

Under normal conditions a temperature which is not very low will produce rather an agreeable sensation; one feels more active, and the respiration becomes better. There is more oxygen taken in and more carbon dioxide exhaled. When the temperature is very low, and the organism is exposed to it for a long time, functional disturbances make

their appearance. At first the circulation becomes more active, and the temperature rises; but soon this excitation disappears, the limbs become numb, and the sight impaired. A general lassitude and an imperative desire to sleep make their appearance; general sensations become obtunded, respiration is difficult, the heart rate is slow, and syncope, followed by death, may ensue.

Before death occurs, the muscular fibres cease to contract voluntarily; the muscles of the neck and of the extremities become rigid, and thus immobilize the body in a position which it had assumed at the time it was overtaken by cold. This explains the bizarre attitudes in which the bodies of individuals who died from extreme cold are found. According to Desgenettes, muscular contractures may spread over the entire body, and epileptiform seizures may carry off the unfortunate victims. It has been also observed that in a certain number of cases the cold air entering the lungs produced excruciating pain and sudden arrest of respiration. In some cases there is a state of delirium with a tendency to suicide.

The degree of cold which is apt to cause death is difficult to determine, because there is a considerable difference in resistance in various individuals. A man in perfect health is capable of tolerating a very low temperature which an individual in a state of fatigue or exhaustion is unable to resist. In Tagetthoff's "*Le tour du monde, 1896*," we see that the crew of the ship lived eight hundred and twelve days in a temperature alternating between 40° and 50° below zero. Other travellers reported similar facts. Adults are able to stand cold provided they are not under the influence of alcohol, because alcohol causes a dilatation of the capillaries and thus facilitates the deleterious effect of cold. *Children* are less apt to resist low temperature than adults, because they produce less heat. Excessive mental and physical work and inanition are also causes of death from cold. It is interesting to note that insane individuals possess remarkable resistance power; they never complain of cold.

At autopsy the muscular tissue is found red; the blood is dark; the heart and bloodvessels are filled with blood; ecchymoses are found on the pleura; the lungs are either anemic or congested. The brain is either anemic or congested. Wichniewski¹ was the first to observe small hemorrhages in the mucous membrane of the stomach. Since then this sign has been considered pathognomonic. Schrimpton observed an inflammation of the gastro-intestinal tract in soldiers who died from cold during campaigns.

The mechanism of death is as yet not satisfactorily explained. According to Magendie, there is a contraction of the peripheral capillaries, with this result, that there is an increase of intravascular tension; congestion of lungs and brain follows. Pouchet thinks that the blood becomes frozen and stagnant in the peripheral bloodvessels, and this leads to embolism in central bloodvessels. According to Horwatt, weakness of the muscular system and of the heart are the main factors in the causation of death.

¹ *Mess. de l'hyg. publ. et méd. lég.*, 1895.

PART IV

DISEASES DUE TO CHEMICAL AND ORGANIC AGENTS

CHAPTER IX

CHRONIC LEAD, ARSENIC, MERCURY, PHOSPHORUS, SILVER, COPPER, ZINC, BRASS, TIN, AND MANGANESE POISONING

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CHRONIC LEAD POISONING

As is indicated in the title, the following discussions will be devoted solely to the *diseases* produced by certain important chemical substances. Acute poisonings, belonging exclusively to special works dealing with toxicology, are not touched upon except insofar as they produce peculiar disease-pictures or are of immediate importance in relation to subsequent symptoms. Many inorganic chemical substances accused of causing disease, but which apparently do not produce any definite symptoms, have been excluded; while zinc and copper, for example, concerning which there is much difference of opinion, have been mentioned briefly.

Unfortunately in America the study of dangerous industries must be carried out almost solely through individual effort. Governmental study of the influence of trade upon health has been extremely fragmentary, and, from a scientific standpoint, usually extremely casual. Extensive governmental study of the question, with a view to exercising reasonable control, is very much to be desired, because there are special circumstances which render some European statistics and laws of doubtful applicability here.

In clinical and economic importance, chronic *saturnism* largely overshadows all other chronic intoxications except that due to alcohol. From the economist's standpoint it is noteworthy that no chemical so readily capable, in its ordinary uses, of causing chronic poisoning, is handled by such large numbers of persons, and none is employed for

such manifold and important purposes. Layet¹ made a list of 111 occupations in which industrial lead poisoning may more or less readily occur. The printers, painters, potters, and earthenware makers in and about Vienna, numbering in all about 44,380, furnish yearly at least 1563 cases of lead poisoning, with 43,045 sick days from this cause alone.

The clinical interest is also wide, for many of these industries furnish products that occasionally cause poisoning in those who use them. Accidental lead poisoning is much less important than industrial, and is less common now than it was a decade or two ago; but its sources are almost innumerable, some of them being evident, some most unexpected, and not a few dependent upon the use of lead in preparations which are of a secret nature and therefore more dangerous because the risk from them is often discovered only through the occurrence of poisoning. The clinical importance of the subject and its complexity are largely increased by the fact that saturnism at times appears in most peculiar clinical guises, and the nature of the condition is extremely likely to be overlooked, particularly if a source of intoxication is not readily suggested by the history.

Etiology.—Race.—Racial susceptibility is not usually recognized, but it is stated that negroes have a distinct tendency to lead convulsions.

Heredity.—That there is a family tendency to lead poisoning is claimed by various observers, particularly Oliver, who saw fatal saturnism in a father and four sons. Fetuses of animals poisoned with lead may have the metal in their tissues, and the finding of large amounts of lead in the organs of a premature infant born of a mother chronically intoxicated with lead, indicate that infants of lead-poisoned mothers may acquire saturnism from the mother direct.

Age.—Those past middle life are more disposed to lead poisoning.

Sex.—Oliver² particularly insists that women show a strong susceptibility to lead poisoning.

Period of the Year.—It is generally recognized that workers in lead suffer more frequently during hot months. The especial frequency of accidental cases due to drinking-water during the summer and autumn has been repeatedly noted, and has been shown³ to be due to the especially acid nature of waters coming from peaty gathering grounds at these periods of the year.

Previous Diseases and Previous Attacks of Saturnism.—Any preëxisting disease that reduces the resistance, perhaps chronic renal trouble especially, increases the liability to attack. The tendency to further attacks, after once suffering from saturnism is very striking. This is usually due to further exposure, but Bernhard especially has dwelt upon the fact that characteristic symptoms may appear without any renewal of exposure. Such instances are apparently due to the escape into the circulation of previously insoluble deposits of lead.

¹ *Poisons industriels*, Office du Travail, Paris, 1901.

² *Dangerous Trades*, New York, E. P. Dutton Co., 1902.

³ *Reports of the Medical Officer of the Local Government Board of Great Britain for 1895, 1900-01, and 1902-03; supplements.*

Habits.—Alcoholism is unquestionably very important in increasing the liability to saturnism, and alcoholic excess frequently determines the actual onset of an attack, particularly of encephalopathy. Sexual excesses are especially insisted upon by Oliver as a predisposing factor, women of loose life suffering particularly. All other depressing excesses, lack of exercise, and unhygienic habits, strongly favor poisoning; but the most important factor of all in a vast proportion of industrial cases is carelessness as to inhaling dust or ingesting particles of lead. In most industrial poisonings, and therefore in the majority of all instances, the lead is actually breathed in or is ingested as a direct result of eating, drinking, using tobacco, or wiping the lips, without properly cleansing the hands.

Occupation.—This is overwhelmingly more important than any other factor and the occupations in which lead poisoning may occur are manifold. Some are naturally much more dangerous than others, the worst being those in which lead is freely handled and in which the exposure is most continuous, and particularly those in which there is much lead dust. In the average American white lead works, 30 out of every 100 workers are incapacitated each year, and 1 out of every 6 or 7 dippers in the potteries suffers in the same way.¹ Bauer mentions the following as the most dangerous: lead mining and smelting; zinc smelting; working in white lead and lead colors; making lead pipes and various other lead objects; making pottery and earthen-ware; type-setting and type-making; working in electric storage-battery factories; file-making; diamond cutting, and polishing gems and semiprecious stones; weaving, especially Jacquard weaving; making tinware; installing gas and water pipes. Of these, file-making and Jacquard weaving may be practically excluded in this country because of improved methods; type-setting seems certainly to produce saturnism only rarely here, because improvements in mechanical methods have largely supplanted handwork; and apparently tinsmithing is not particularly dangerous at present, owing to improvements in solder and in general hygienic conditions. Installing gas and water pipes is certainly not a common cause, but it may be dangerous in large operations. The other occupations mentioned by Bauer are all dangerous here. Poisoning in miners occurs principally in carbonate mines, and not in those in which chiefly the sulphide is present, a fact that is usually considered to be due to the insolubility of the sulphide. This is at least partly due to the fact that carbonate mines are likely to be dry, and therefore more dust is produced in them, while sulphide mines are often wet; and the water in the latter usually contains sulphuric acid, which prevents formation of the carbonate from the sulphide. Smelting ores containing lead is dangerous, particularly when the ventilating apparatus is not perfect, as the heat produced in smelting undoubtedly adds to the danger by increasing the motion of the atmosphere and hence the production and intake of lead dust.

Of all occupations the manufacture of white lead and of lead colors

¹ From the figures of Alice Hamilton.

furnishes the greatest proportion of cases; though electric storage-battery makers, and, in potteries, those engaged in dipping the ware into the glaze and handling it immediately afterward, in spraying decorative glazes, and in dusting on pigment in the decalcomania process, are in practically as much danger as lead workers. The possible dangers in white lead works are shown by Kaup's figures for the Bleiberg Lead-worker's Union in Klagenfurt. In 1894, the 45 members showed 61 attacks of lead poisoning (135.6 per 100), and the average per man, was 46.7 sick days in the year. In Herbert's works, in the same town, the attacks each year, per 100 workers, have ranged from 13.2 to 24.6. The influence that has apparently been exerted by careful regulation of this industry in France is seen in the statement of Leclerc de Pulligny that although Paris and Lille are the centres for the production of white lead in France, the cases of the lead poisoning in the hospitals of Paris among those employed in this occupation numbered only 13 in two years. The English and German statistics are equally creditable.¹ Electric storage-battery factories, though not numerous, are very dangerous, unless they are well conducted. At the Episcopal Hospital in Philadelphia there were 23 cases in the wards in a little over two years from one factory and many others in the out-patient department (Edsall).

Painters are common sufferers, and usually in inverse proportion to their cleanliness, intelligence, and skill. A considerable number of the skilled artisans, however, always suffer.

Among others in some danger are the makers of rubber goods, particularly among the heavier kinds, and of glazed and enamelled metal ware; glaziers, ship builders, sailors, laborers in structural iron works (handling freshly painted iron), Bessemer steel workers (Ormerod), workers in brass foundries and occasionally in other foundries, makers of the modern "secession" bric-a-brac, etc.; lace and passementerie makers, and workers in silk mills (when the silks are weighted with lead).² Poisoning among workers from lead dyes was once rather common; lead chromate is still used a little, but this is now of insignificant importance. In the Episcopal Hospital in Philadelphia, in the midst of vast textile industries, there were no industrial cases in women in a period of five years, and among the 98 industrial cases in the men's ward in this time there was but a single weaver, and this man was probably poisoned from another source (Edsall).

In any obscure case the details of the patient's occupation should be investigated most minutely, for occupational sources of lead poisoning are multitudinous and often utterly unexpected.

Accidental Poisoning.—Detailed investigation of many points is often necessary in this instance, both to determine the source and do away with it. Water is, of course, the most common source, though its frequency has been distinctly lessened by the considerable reduction in

¹ Legge and Goadby, *Lead Poisoning and Lead Absorption*. Alice Hamilton, *Trans. Chicago, Path. Soc.*, 1909-1912.

² For recent conditions in Austria concerning this point see Kaup, *Gesundheitsgefährliche Industrien*, etc., 1903, Fischer, Jena.

the use of lead pipes for public and particularly for private supplies. Drinking-water becomes poisoned in a number of ways. The carbonic acid in rain- or spring-water may be the cause of poisoning, especially when new lead pipes are in use, soluble acid carbonate being formed; a deposit of relatively insoluble basic carbonate is gradually formed on old pipes, and acts as a partial but not absolute protective. Power and Houghton emphasize two especial causes: one of them a direct oxidizing or "erosive" action due to oxygen in solution in the water, the other the formation of soluble salts of nitric, nitrous, or organic acids; and of these, they consider the latter to be of much the greater importance.

Lockhart Gibson makes an interesting suggestion concerning the almost epidemic poisoning of the Queensland children by ingestion of lead from painted woodwork of houses; he found appreciable quantities of lead in the dust collected in rooms and also on the hands after they had been rubbed over painted surfaces, the children affected almost always were those who bit their nails or sucked their thumbs. Sleeping in freshly painted rooms has occasionally been the cause, the lead in this instance being inhaled and apparently carried by the turpentine vapors. Poisoning of women, practically epidemic in its extent, has been observed from washing the clothes of lead workers. Glazed earthenware and enamelled metallic vessels which are used for cooking and preserving foods, have caused poisoning, though this is uncommon now with the better grades of such vessels in use. Formerly the lead in the solder or the tin made the eating of canned goods, or the use of tin vessels for acid foods, somewhat dangerous, but the risk is now minimal owing to improvements in the tin, the solder, and the methods of sealing; and the actual number of cases known to have been poisoned in this way, even in earlier years, is small. Because of its cheapness, lead is, however, sometimes used in the making of drinking vessels and, in earlier times, caused many cases, especially when such vessels were used for cider, wine, or other acid beverages. Variot has recently reported saturnism in a child from this cause. Children's toys, when made of lead, have caused poisoning, and the same may occur when they are colored with lead pigments, though the latter are probably now used but little for this purpose. Candies were at one time colored with lead dyes, but this is rare at present; and the use of lead chromate in baker's products has hardly been heard of since Marshall showed how common it was in Philadelphia, and D. D. Stewart¹ demonstrated a most dangerous epidemic from this cause. Foods in general are so carefully watched now that there is little danger from them directly, though epidemics are still occasionally reported in Europe as a result of "filling" mill-stones with lead, the lead being gradually ground off into the flour. The opportunities for such an occurrence in this country have been eliminated by the advent of roller mills. Soda water or carbonated water in siphons may cause poisoning, particularly if the tanks, the siphons, etc., are made of lead; and Cao has recently found lead in carbonated water in siphons, and reported a series of poisonings

¹ *Medical News*, December 31, 1887; and *Third Annual Report State Board of Health of Pennsylvania*.

due to this cause; there is little danger from this source in this country, as block tin and zinc have almost completely supplanted lead for this purpose. Cosmetics, hair dyes, and false teeth are commonly known to have been sources of poisoning. Medicinal lead poisoning was known to the physicians of the ancients; it is generally thought to be very uncommon now, but Miller¹ reported two personal observations and discussed a series collected from the literature, and he thinks that slight or moderate symptoms from this cause are probably not infrequent. The use of diachylon ointment over large eczematous surfaces is certainly dangerous, and has caused fatal poisoning in infants (Passler, Hahn); and poisoning from internal use of diachylon as an abortifacient has also been repeatedly observed in England (Ransom).

Infants have been poisoned by dusting powders containing lead, or by cosmetics or ointments used on the person of the nurse.

The duration of exposure before the development of plumbism has naturally varied greatly. This is attributed to variations in individual susceptibility. A certain degree of immunity undoubtedly exists in some persons, others are certainly especially susceptible, and intercurrent factors are known to increase or decrease susceptibility.

Accidental or medicinal ingestion of single large doses has frequently caused somewhat prolonged poisoning, usually colic, though encephalopathy has repeatedly, and paralysis in rare instances, followed a single dose or a few doses. Colic and indefinite symptoms of poisoning often occur soon after beginning work in lead. Tanquerel repeatedly saw wrist-drop after a week's exposure, and others have had similar experiences. As a rule marked colic does not occur for several weeks or longer, and symptoms of poisoning may first appear after even many years of exposure. Paralysis is usually rather a late development, commonly appearing only after preceding cachexia or colic, and therefore after prolonged exposure. Encephalopathy is not infrequently seen within a few weeks or months, but often arises late.

Pathology.—This is not characteristic. There is usually general emaciation; the teeth of many members of the laboring classes are often in bad condition and in such the blue line may be found. Arteriosclerosis is regularly found in the subjects of saturnism. Chronic gastroenteritis is common, but no special changes have been described in the digestive tract except pigmentation of the walls of the intestine with lead sulphide and degeneration of the cells in the ganglia of the intestine. In experimental cases (Oliver) the intestine is often found in extreme spasm. A considerable number of observers have noted nephritis in the early stages and have produced it experimentally. In old cases interstitial nephritis is a very usual lesion, often the most important. In a small proportion of cases the lesions of gout are present.

In cases with nervous lesions, the paralyzed muscles are more or less atrophic and show degeneration of the muscle cells and minute hemorrhage between the fibres. The peripheral nerves, whose territory was involved clinically, have been many times investigated and always

¹ *Therapeutic Gazette*, 1904.

found degenerated and have shown in addition small hemorrhages in the nerve sheath and between the fibrils. In the eye, vascular spasm and anemia can be seen as the cause of cases of acute transitory amaurosis; obliterative endarteritis, followed by swelling of the disk and atrophy of the nerve, is the lesion in permanent blindness. The motor cells of the anterior horns of the spinal cord may show changes; clumping or solution of the Nissl bodies is described; the cells themselves may even shrink and disappear. The usual gross cerebral lesions in encephalopathy have been œdema and anemia, flattening of the convolutions, thickening of the pia, and small hemorrhages. Microscopic studies show marked changes of the cortical cells, hemorrhages, and proliferation of the cell nuclei in the vessel walls and of the glia cells about the vessels.

Mode of Entrance and Pathogenesis.—There are three channels of entrance commonly spoken of: the *respiratory*, the *gastro-intestinal*, and the *cutaneous*.

The well-known conditions of anthracosis and pneumokoniosis, should have made us realize that lead dust could easily reach the lungs and be there absorbed; the occurrence of many cases of colic in the mining and smelting industries shows that lead (chloride) fumes are capable of causing poisoning. Prevention of dust and removal of fumes, by exhausts, in the handling of powdered or fuming preparations of lead are followed at once by a diminution in the number of cases of plumbism. "A lead salt is poisonous in direct proportion to its dustiness."

Small amounts of lead are doubtless constantly ingested by lead workers; the water-borne epidemics and cases following the administration of lead give the most unquestioned examples of gastro-intestinal origin; in the empty stomach, lead chloride is probably formed, which lower down is easily absorbed. On the other hand, the mixture of food and ingested lead results, in part at least, in the formation of insoluble peptonates and albuminates.

The skin probably admits but little lead into the system; a few cases of lead poisoning have followed the continued use of hair dyes, and lead plasters; it is not now considered that absorption through the skin of the hands affects the radial nerves directly.

The greatest amount of lead has been found in the liver. Only minute quantities are found in the kidneys; the brain, cord, nerves, muscles, bones, and other tissues contain various amounts. In many instances the brain contains little or no demonstrable lead, even in encephalopathic cases.

The manner in which lead acts is in many points still a subject of controversy. Colic seems to be due to spasm of the bowel, dependent most probably, but not certainly, upon changes in the intestinal ganglia. The changes in the muscles, together with the peculiar localization of the paralysis and the absence of sensory symptoms, suggested the view, that is still not wholly disproved, that the paralysis is spinal in origin, but most observers and investigators now lean to the view that the peripheral changes are primary. The constancy of peripheral changes, and the infrequency of noteworthy changes in the cord, make the peripheral the more probable theory. It seems probable (Edinger, Teleky) that

the peculiar distribution of lead paralysis, represents a "playing out" or exhaustion of those nerves and muscles most called upon in the performance of the various movements required in the different trades or activities; painters get wrist-drop early, file-makers show atrophy of the interossei, workers in the trades requiring heavy lifting are more apt to show affection of the shoulder muscles. Recent studies dwell upon the occurrence of marked inflammatory degeneration in the minute arteries, leading to rupture of their coats and hemorrhagic infiltration of surrounding tissues.

A small amount of lead is excreted through the kidneys and it is partially excreted in the feces. A little excretion occurs through the sweat, but this is of slight importance. It has also been found in woman's milk (Bulland), a fact of interest in relation to the infants of lead-poisoned women. Lead has been demonstrated in the parotid glands and saliva. The minimum dose capable of producing poisoning when long-continued is not clearly determined. Brouardel considered that 1 milligram daily may suffice.

Symptoms.—The clinical course of plumbism consists, in most instances, of the development of more or less marked but indefinite general symptoms, followed after a variable time, usually at least several weeks, by the appearance of colic. Less commonly, but still frequently, paralysis supervenes; occasionally the graver cerebral manifestations occur, usually after some previous colic. There is no constancy in the course of the symptoms; violent colic may be the first manifestation soon after exposure begins; paralysis may develop very early; and in rare cases, without preceding noteworthy symptoms, coma, or an outburst of convulsions or of more or less dangerous delirium, may be the first recognized evidence of poisoning; occasionally indefinite ill health without distinctive symptoms lasts for years and ultimately causes death, usually chiefly from chronic renal disease.

It is important to recognize that preceding general symptoms are practically always present. The earliest manifestations of these are from the blood and vascular system. A curious sallow pallor, with a marked wasting of the subcutaneous fat and a slight actual anemia, gives the well-recognized picture of lead cachexia. Loss of appetite, gastric distress, a metallic taste, furred tongue, offensive breath, with constipation or diarrhœa, are frequent, early, general symptoms of an affected digestive system. Insomnia, restlessness, mental and physical depression and weakness, are common nervous symptoms preceding the severer later conditions. A persistent slight rise in the blood pressure, pains in the limbs and trunk, weakness of the muscles to be later paralyzed, are other fairly constant early signs. At any time, however, the more distinctive characteristics of lead poisoning, colic, paralysis, or cerebral symptoms, may appear with the general symptoms. Colic almost always develops and usually soon after the first signs of ill health. Paralysis, when it occurs, commonly comes on after some cachexia has appeared; that is, after poisoning has lasted for a considerable period. Encephalopathies may develop early if the poisoning has been severe, but they likewise may occur later.

Two conditions, the basic granulation of the erythrocytes and the blue line on the gums, are usually present at an early stage of poisoning, and often when there are not actual symptoms of intoxication. Basic granulation, so far as is known, is constant during the whole time that lead is present in the system, and it appears even when exposure has been extremely brief; White and Pepper¹ found it after four days' industrial exposure, and even twenty-five hours after a single dose of $7\frac{1}{2}$ grs. (0.5 gm.) of lead acetate. Neither of these signs alone constitutes absolute evidence of clinical saturnism, and basic granulation is found in many other conditions; but both are of extreme importance in suggesting that lead is being absorbed, and are valuable confirmatory facts in the presence of obscure symptoms. The blue line, when characteristic, is certain evidence that lead has been absorbed; while basic granulation is only extremely suggestive.

The *blue line*, sometimes called Burton's line, was first studied clinically by Burton in 1834, and practically at the same time by Tanquerel. Clinically it appears to be an irregularly linear or broader, dark blue discoloration of the margin of the gum. Close inspection shows that it is frequently a line's breadth from the edge of the gum, though if the latter is loosened and overhanging or is atrophied, the line is often on the very edge. It may appear stippled even to the naked eye, and a hand-lens shows that it is made up of fine, nearly round dots, which are sometimes discrete, sometimes closely clumped together. At times it consists of a few isolated dots or of a very slight and ill-defined line, especially if the gums and teeth are in good condition. It is not usually continuous from one tooth over to the next; the portion of the gum situated between the teeth shows it most commonly, but little separate arches, or partial arches, may form over the bases of the individual teeth. It is especially marked about the incisors and canines, and particularly in the lower jaw. This line is due to deposits of lead sulphide in and about the epithelial cells, already swollen and loosened as a result of gingivitis. "The lead sulphide is undoubtedly due to decomposition of lead salts in the mouth by the sulphureted hydrogen produced by decomposition and putrefaction of food, epithelial debris, and other materials which have accumulated about the edges of the teeth, and in the interdental spaces." (Legge and Goadby.)

Basic granulation of the erythrocytes gives the appearance of a stippling, with granules that vary in size from fine points to others as large as eosinophilic granules; it is evident only after staining, the granulations taking basic stains. They are seen in many different diseases, but it is important to note that in lead poisoning they are constantly present, are usually seen in many erythrocytes, individual cells often show large numbers of them, and the granules are ordinarily of rather large size. They apparently persist throughout the whole course of poisoning, and vanish soon after lead disappears from the system (White and Pepper), though this point is one that has not been sufficiently studied.

¹ *Contributions from the William Pepper Laboratory of Clinical Medicine*, 1901.

Together with the basic granulation there is usually some anemia, but the counts rarely show the red cells below 2,000,000. There is some reduction of the hemoglobin; usually not severe and rather less than is proportionate to the decrease in red cells. Nucleated red cells are frequently present in small numbers. Gilbert finds eosinophilia common in the earliest stages.

When actual symptoms of poisoning appear they are both general and local. Slight fever (99.5° to 100° F.) is present in unusual cases, and at times may be somewhat prolonged; this may cause confusion in diagnosis. The most important local clinical effects are as follows:

Digestive Tract.—Anorexia, an unpleasant sweet or metallic taste, furred tongue and offensive breath, are frequently complained of in the beginning, and the last symptom is often extreme in well-developed poisoning. Nausea and vomiting are very common (Tañquerel, Stewart); Oliver has especially noted attacks of epigastric pain which may be violent. Constipation is the rule, and is frequently extremely obstinate, especially when colic has developed; occasionally constipation alternates with diarrhoea, and rarely there is persistent diarrhoea. Among rarer disorders of the digestive tract are salivation, severe stomatitis, parotitis, and ulcerative colitis.

Colic is the symptom of chief importance referable to the digestive tract. It is, however, not due to disturbed digestion, but apparently to spasm of the bowel of nervous origin. In severe accidental poisoning, colic may appear after a single dose, and occasionally in industrial poisoning within a few days. Usually weeks or months of poisoning and frequently similar periods of indefinite ill health precede it. Generally the patient has been constipated beforehand, often severely so, and commonly forebodings of pain have already been felt when the first attack of actual colic comes on. Severe pain then appears, often in the night, generally below the umbilicus, in frequent paroxysms lasting for a few seconds or minutes, in some cases even for hours. The severity of the pain varies; at times it is extreme, and the patient is in restless agony, cold, pallid, sweating, and almost collapsed from suffering, with a small pulse of high tension and remarkably slow. The abdominal walls are usually hard and retracted during the paroxysm, and pressure upon them gives relief. Vomiting is common during the paroxysm and constipation is usually most obstinate until the spasm of the bowel is over. Frequent endeavors to defecate result only in the expelling of a little mucus. The secretion of urine is much reduced. The duration of an attack, with the paroxysms and remissions, is sometimes a few hours only, more commonly several days, frequently ten days or a fortnight. The severity, however, usually decreases continuously after the first day or two of treatment. Recurrences are the rule if exposure continues; they may occasionally develop long after exposure has ceased.

Respiratory Tract.—Aphonia and dyspnoea from laryngeal paralysis have occurred. Asthma is an occasional though uncommon result of the intoxication. Pulmonary tuberculosis is unduly common in subjects of plumbism, partly as a result of inhalation of irritants, partly from reduced general resistance.

Cardiovascular System.—Arteriosclerosis is common in lead workers even at an early age. A considerable number of those poisoned for a long time ultimately exhibit the symptoms of cardiovascular incompetency, and die from circulatory failure, or occasionally from cerebral accidents.

Genito-urinary System.—A slight degree of albuminuria with some casts is not uncommon in the early stages, especially if the dosage has been large. Albumin and casts are frequently present during an attack of colic. After prolonged poisoning, progressive interstitial nephritis often becomes the most important feature of the case, and it is probably the commonest late cause of death. Suppression of urine, spasm of the bladder and urethra, and sometimes retention of urine, may be seen with colic. The influence upon the generative organs is seen chiefly in women. Menstruation becomes disturbed, being usually excessive and irregular; and pregnant women with saturnism are extremely likely to abort or to have premature labors. In the latter case the child is often stillborn, or it is very frail and usually soon dies. After exposure has ceased, women often pass through repeated normal labors.

Arthritis.—Gout occasionally occurs, but it seems that other predisposing causes are necessary in addition to plumbism. Goadby notes that gout when seen in connection with lead workers is usually in those who work with paints, and suggests turpentine as the cause of the gouty manifestation. Saturnine gout is apparently somewhat peculiar in that it involves joints ordinarily spared; the rapidity, too, with which many joints are attacked is often striking.

Nervous System.—Moderate pain, often indefinitely located, is common in both the extremities and the trunk, especially in early stages. Minute hemorrhages in the nerves are the probable cause of these neuralgic pains, and also of the joint pains. Pains in the joints appear in intermittent paroxysms, which may be very severe and may last for days. They are usually most marked in the knees or ankles. The muscles sometimes ache severely, and may be tender, especially those that are soon to become paralyzed. Other sensory symptoms are usually slight. There may be paresthesias, and general sensation may be reduced or lost over the back of the forearm, less commonly over the front of the leg or other localized area. Hyperalgesia is occasionally noted, and in rare instances there is much tenderness over the nerve trunks. Sometimes actual hysterical symptoms are present, with hemianesthesia or other characteristic stigmatic local areas of anesthesia. Cerebral accidents (hemorrhage, etc.), if they occur, may produce hemianesthesia.

With the diffuse pains, certain muscles, particularly those of the calves, may go into mild or severe cramp. This seems to be particularly the case in children (Turner). Fibrillary twitching of the affected muscles is common after paralysis has developed. Tremor is frequently noted, especially in old cases. It affects chiefly the hands, and is usually of slight amplitude and not striking, though it is sometimes coarse and may resemble the tremor of paralysis agitans.

Most important of all the nervous symptoms is paralysis; in its usual distribution it is of itself almost distinctive of lead poisoning. When

typical, it produces so-called "wrist-drop," and "toe-drop," which is bilateral. There is at first an increasing degree of weakness in the extension of the fingers at the metacarpophalangeal joint (paralysis of the *extensor communis digitorum*), followed by weakness and often complete paralysis of the extensors of the wrist. Palsy often begins in one hand, the other following within a fortnight or less; frequently the hand first involved has been subjected to special strain. The paralysis is usually subacute in its onset, reaching a marked degree within from a few days to a fortnight; occasionally it progresses very slowly. In "wrist-drop," the "antibrachial" type of paralysis, the hand is in flexion at the wrist from paralysis of the extensors, with unopposed action of the flexors, and the fingers are similarly moderately flexed, owing to paralysis of their long extensor. At first, the distal phalanges can be extended if the proximal phalanges be first passively extended, for the *interossei*, the proper extensors of the distal joints, are then uninvolved; the thumb muscles, the *extensor indicis*, and *extensor minimi digiti* also usually functionate at first. Later, these extensors, the *interossei*, and the muscles of the thumb are affected; distal extension of the fingers and extension and adduction of the thumb are imperfectly performed, or impossible. The long abductor of the thumb often becomes involved late, but in early stages is usually spared; and the *supinator longus* is almost never included in the common type of paralysis, a point that is of great importance. The distinctive characteristics of this paralysis are, that it is almost always bilateral, is purely extensor, spares the long *supinator* and usually the long abductor of the thumb, and there are rarely any sensory symptoms, except, perhaps, limited cutaneous anesthesia over the backs of the forearms. Atrophy begins soon in the affected muscles, especially those of the back of the forearm; marked reduction or loss of faradic response appears; and the reactions of degeneration develop. As a rule, some of the muscles other than those distinctly paralyzed are weak, and may even show the reaction of degeneration. The paralysis ordinarily soon reaches the limit of its intensity and extent. Fresh cases quickly improve within a few weeks after proper treatment is started, and generally recover almost completely within a few months if they are not extremely severe. In older cases recovery is slow, and dependent upon the grade of the palsy and its duration: if long neglected and severe, complete recovery is not common, and occasionally very little improvement occurs.

Forms of paralysis other than characteristic wrist-drop may occur. The Aran-Duchenne type is occasionally seen; in it the small muscles of the hand, the *interossei*, and the thenar and the hypothenar early become atrophied and more or less paralyzed, and these changes produce the "simian" hand. This is not a clearly individualized type in lead poisoning, being usually associated with the previously described form. The Aran-Duchenne form has been particularly noted in persons whose occupation, such as file-making, causes a special strain on the small muscles of the hand. The upper arm, the brachial, or Duchenne-Erb type, in which the deltoid, often the biceps and the *brachialis anticus*, and sometimes the *supra-* and *infraspinati*, are involved, occurs occa-

sionally, particularly in those whose work requires heavy lifting. In it the arms hang by the side, rotated somewhat outward and incapable of abduction, and in severe cases incapable of flexion at the elbow. This form has repeatedly been seen as a separate condition, though it is usually associated with paralysis of the extensors of the fingers and wrist. Contrary to the conditions in the ordinary forearm type, the supinator longus is likely to be involved in this variety. Of this group of muscles, the deltoid is especially liable to paralysis, and it has repeatedly been the sole muscle palsied; sometimes it has been paralyzed on one side only.

The lower limbs are infrequently affected in adults, and, when they are, the arms usually suffer also; the conditions in children differ markedly in this point, as will be noted later. In the legs, the peronei and the extensor of the toes are the typical seat of paralysis, the tibialis anticus, like the supinator longus in the arm, almost always being spared. In rare instances in adults, more commonly in children, the tibialis anticus is paralyzed, while the muscles usually affected escape. The disease, in the legs, as in the arms, is practically always bilateral. The small muscles of the feet occasionally show special involvement. Rarely the disease is situated chiefly in the muscles of the thigh. The knee-jerk may be increased when the legs are affected; it may be normal; sometimes it is reduced or lost.

Paralysis of the cranial nerves is occasionally noted. The nerve most frequently involved is the optic, though fortunately this is rare; the eye symptoms will be mentioned later. Laryngeal paralysis is even more rare. The paralysis has most commonly affected the adductors and caused hoarseness or aphonia, though the abductors have repeatedly been paralyzed and produced marked inspiratory dyspnoea. The facial nerve has several times been paralyzed. Other cranial nerves that have certainly been separately paralyzed as the result of lead, are the abducens and the oculomotor; paralysis of these nerves, as of the optic, is commonly associated with cerebral signs. Sometimes several ocular and other cranial nerves have been involved coincidently. Ophthalmoplegia has occurred.

In addition to the localized forms of paralysis, cases are occasionally seen in which generalized paralysis appears, usually advancing from the periphery toward the trunk. In these instances it is probable that both spinal and peripheral changes are present. There are two important varieties: one occurring acutely the other progressing slowly. Fever may accompany the acutely occurring form. Both ordinarily end in recovery. Very rarely death has occurred from asphyxia. In rare instances, paralysis of the diaphragm has occurred, even without general palsy. A few cases have been seen of diffuse paralysis following the type of progressive muscular atrophy. Some cases have been observed in which conspicuous ataxia, absent knee-jerks, and very slight paralysis, produced some resemblance to locomotor ataxia. Putnam, Bechtold, and Oppenheim report cases resembling spastic spinal palsy, with the presence of lead in the urine.

Cerebral Symptoms.—*Encephalopathy.*—Transitory hemiplegia, aphasia and choreiform movements have been occasionally seen. There may

be hysterical symptoms, "toxic hysteria," with hemianesthesias and other stigmata, or hysterical outbreaks of excitement or convulsions, especially in predisposed young women. Late in the course of old cases, nephritis and arteriosclerosis may cause apoplexy, with persistent hemiplegia or other cerebral lesions.

The most common and striking cerebral symptoms are epileptiform convulsions, mania, delirium, and coma; sometimes a picture more or less closely resembling parietic dementia. In Tanquerel's 1217 cases, encephalopathy occurred 72 times. Its frequency varies according to the dose, and perhaps according to the nature of the lead compound ingested. In Stewart's chrome-bun series of 64 cases, encephalopathy occurred 15 times. These latter figures are, however, perhaps partly due to the fact that many children were affected. The outbreak often comes suddenly; alcoholics are especially liable. Convulsions, or less commonly delirium, usually occur first. Coma may follow. The convulsive attacks are epileptiform with clonic and tonic movements; only one may occur, but, as a rule, the attacks are repeated at varying intervals over days—rarely, even weeks. Epileptiform attacks have occasionally persisted. In the delirious form the patient may be very violent; convulsions not uncommonly interrupt the delirium, and there are often striking changes from violent intellectual and motor activity to hebetude and quiet. Delusions of persecution and particularly hallucinations, especially of terrifying character, are common; though they are not confined to such subjects, hallucinations are very frequent in those who are also alcoholic, and with marked tremor the resemblance to delirium tremens may be very striking. Fever (100° to 101° , occasionally even higher) is not uncommon. The duration may be extremely brief, but more commonly delirium lasts from several days to a fortnight or sometimes longer; in unusual instances the patient remains insane. The fact that delirium may be of sudden and violent onset is at times one of grave moment. Acute encephalopathies are very dangerous; Tanquerel saw 16 deaths in 72 cases, and as a rule the mortality is put higher than this. Death usually occurs in convulsions, in coma, or from general exhaustion.

Symptoms of general paresis have been observed in a considerable number of cases. The onset is, however, more rapid and speech is less disturbed than in ordinary parietic dementia, moral vagaries are less common, and recovery often occurs even from extreme states.

Eye Symptoms.—Disease of the external ocular nerves produces the corresponding muscular paralyses. Nystagmus has been observed. Hemianopsia, usually homonymous, may appear rarely. Transitory blindness may develop suddenly, usually in encephalopathic cases; this blindness commonly disappears rapidly and completely. Vision may gradually become impaired, with the symptoms common in other forms of amaurosis, and, of these, probably at least one-half show persistent structural changes in the optic nerve (de Schweinitz). Ophthalmoscopically, the transitory cases may show nothing; the changes found in other cases are those common in amaurosis, except that lead subjects show especially marked vascular lesions; and it is also noteworthy that in optic

neuritis the lesions are not confined to the parenchyma, as they are in the nerves of the extremities, but are also interstitial and perineuritic. Serious eye symptoms are fortunately rare in this country; de Schweinitz saw only three instances in over 15,000 eye cases.

Lead Poisoning in Children.—Plumbism in infancy and early childhood commonly shows some clinical divergence from that in adults, and a brief mention of it is demanded. It is, naturally, not common in the very young, since it is always accidental in them.

Symptoms.—It is possible that some of the sickly, nursing infants of mothers with plumbism have lead poisoning and die of it. Infants seem prone to convulsions when poisoned by lead. Colic, pains in the legs, and cramps in the muscles are commonly noted symptoms. In older children there is a striking frequency of cerebral symptoms, such as convulsions, retraction of the head, rigidity of the neck. Meningitis is often suspected, and Turner and Gibson refer to the marked frequency of ocular paralyses and optic neuritis. In paralysis in children the legs are almost regularly affected; a further peculiarity, as compared with adults, is noted by Turner, the peroneal muscles usually affected in adults often escape, while the tibialis anticus is usually paralyzed.

Ocular Symptoms.—Paralysis of the abducens and the oculomotor nerves, ophthalmoplegia and blindness are often observed; sometimes the latter disappears, and sometimes it becomes permanent from progressive optic atrophy. Gibson's term "ocular neuritis," is expressive.

Diagnosis.—Proper knowledge of the sources of lead poisoning, and alert attention to details in the history indicative of exposure, will often give an immediate suggestion of the nature of the case, even when the symptoms are unusual. Cachexia, colic, wrist-drop, and toe-drop are of course the most common results of lead absorption and, when characteristic, are sufficient to bring up the diagnosis at once. Their association with a clear source of poisoning, and especially with a blue line, makes the diagnosis practically certain. The absence of a known source of lead is not of much diagnostic importance if the other signs are definite; and, even if the blue line is absent (which is unusual), bilateral wrist-drop without involvement of the supinator longus, and with no affection of the flexors and no noteworthy sensory symptoms, is nearly decisive, though to be completely so it needs confirmation through finding lead in the urine. The search for lead in any case should be undertaken early in the treatment and after giving potassium iodide for a few days. The slight and fragmentary forms of the blue line, which may require a lens to determine their nature accurately, should be carefully sought when a more characteristic line is absent. Basic granulation that is very marked (with hematoxylin-eosin or thionin stain), and that is not associated with profound changes of other kinds in the blood cells, is extremely suggestive and may lead to a correct diagnosis.

Cerebral cases and the slight or more unusual forms of paralysis are much more likely to be misinterpreted. General paresis, epilepsy, any toxic mania, coma, or delirium may be suspected. In children showing "ocular neuritis" and retraction of the head, with stiffness of the neck, meningitis may be diagnosed (Gibson), or poliomyelitis, tabes, spastic paraplegia,

and muscular dystrophies acutely simulated. When convulsions or eye symptoms are present the possibility of uremia must be considered. If the cases are of industrial origin, attention to the nature of the occupation usually suggests the diagnosis quickly, and a search for the blue line, for basic granulation and evidences of cachexia may furnish more direct evidence. It is to be remembered, however, that none of the latter signs constitutes final evidence that unusual varieties of paralysis are due to lead, and if distinctive symptoms are absent, or a source of poisoning is not known, recourse must always be had to examination of the urine; and in any doubtful case the diagnosis must depend upon this. The chief source of error in the blue line is in the fact that it may persist even for years after lead poisoning has disappeared, and it may, therefore, be present with other conditions that have developed later. In cases with only general symptoms the finding of lead in the urine is the sole reliable source of diagnosis. The only satisfactory method is to oxidize the organic matter by heating as much as 500 cc. of urine with one-tenth its amount of hydrochloric acid and two or three grains of potassium chlorate, subsequently driving off the chlorine and concentrating by evaporation. The lead is then recovered by electrolysis, or, as sulphide, by means of hydrogen sulphide.

Prognosis.—General disorders that have not caused serious organic lesions, colic, and the mild and recent palsies, recover entirely under proper treatment. The older and more severe forms of paralysis have a prognosis as to complete recovery that is directly related to their duration and intensity, severe protracted cases rarely getting wholly well. Persistent atrophy and progressive decrease or entire loss of response to electricity are bad signs. Cerebral symptoms are always dangerous, coma being particularly so; if, however, the patient escapes death from encephalopathy, serious consequences rarely follow. Eye symptoms, of slow onset especially, are of very doubtful prognosis. About half of them have persistent optic atrophy, and this goes on to blindness in a large proportion of cases.

The prognosis as to future attacks depends almost entirely upon the discovery and exclusion of the source of poisoning, renewed outbreaks from old lead deposits in the body being very unusual. If the exposure continues, recurrences are probable and are of worse prognosis than the original attacks.

In renal, cardiovascular, and other changes resulting from lead poisoning, the prognosis is dependent upon the severity and stage of these lesions. If the further absorption of lead is stopped, the progress of the lesions that have resulted is, of course, slower.

Prophylaxis and Treatment.—Were the industries that cause exposure subjected to reasonable regulations and these actually enforced, and were the workmen also given opportunity to keep themselves clean, and required to do so, industrial lead poisoning would largely disappear.

Prevention of *dust-inhalation* is the most important part in prophylaxis, and the most difficult to carry out, owing to the carelessness of most workmen and indifference on the part of employers. Much of this is due to a lack of proper comprehension of the dangers and the methods

of avoiding them. The regulations existing in a number of European countries¹ are examples of what should be done; the most important of these regulations are those that demand certain forms of ventilation, height of ceiling, isolation of the most dangerous parts of the work from the other portions of the plant, apparatus for the exclusion of dust or for the removal of that which escapes into the atmosphere, daily cleansing, and such construction of the walls and floors as to permit of easy and thorough cleaning, the provision of separate eating-rooms and of free baths, the exclusion of women and children from the dangerous parts of the work, limitation of the hours of work and of continuous exposure of the same individuals to the most dangerous parts of the work, and the services of a physician who has power to "lay off" any suspicious cases from work and who must report such cases. In some countries it is also required of the workmen that they change their clothes and bathe after working, wear gloves or rub their hands with grease when at work, and do not eat, drink alcoholic beverages, or smoke or chew tobacco in the work-rooms. The enforcement of these laws is sometimes unfortunately lax.

Of the simpler preventive measures, proper cleansing is by far the most important. Respirators are of little use because the men usually will not wear them; sulphuric acid lemonade is of some value, though lead sulphate is absorbed to a slight extent. Theoretically proper, and practically very valuable, is the free use of protein food before beginning work or at mid-day; milk is provided free in a considerable number of plants, and in several it has gained the reputation, which is too favorable, of being an almost certain preventive. Fats, such as olive oil, also seem to have some preventive action. Exercise in the open air, by increasing eliminative functions and general resistance, has a most important influence; companies owning their workmen's houses have built them at a distance in order to necessitate a daily walk to and fro, and with very beneficial results.

When poisoning has developed, exclusion of the source is the first imperative necessity. In industrial cases this means, of course, a change of occupation, or, if necessary, cessation of work; in accidental poisoning it often means painstaking and extended search for the source.

The active treatment consists in elimination of the lead and of general products of metabolism, and in combating general or local symptoms. The initial action in any case should be to expel any lead present in the gastro-intestinal tract, preferably by means of saline purges; purgatives that act largely through increasing peristalsis should not be used. Purgation is frequently difficult to accomplish, for the constipation is often obstinate if there is colic and sometimes when there is not. In such cases it is often necessary to use large and frequent doses of salines (which may have to be combined with simple enemas, or enemas containing a half ounce or an ounce, 15 to 30 gm., of magnesium sulphate), and to

¹ See *Gesundheitsgefährliche Industrien*; Fürgau, *Gifte und Stark Wirkende Arzneimittel*, Haering, Berlin, 1901 (German laws, etc.); *Poisons industriels*; *Dangerous Trades*, ed. by Oliver.

give with the purgatives, to control the intestinal spasm, moderate doses of atropine, pilocarpine, or other antispasmodic. Large oil enemas are also very useful and entirely harmless. In cases with severe colic a movement may sometimes be secured only by giving moderate doses of morphine before the purgatives. Control of the constipation is one of the most important features of the treatment of colic, and colic is the commonest symptom demanding treatment. After the bowels are once opened they should be moved at least once (better two or three times) a day until the local symptoms disappear, in order to encourage elimination and prevent return of the spasm. Water should be drunk freely, and diuretics given if the secretion of urine is low. After the bowels have been moved, potassium iodide should be given in doses of 5 grains (0.3 gm.) three times daily. If increased beyond this it should be carefully watched, as some observers believe that it may temporarily exaggerate the symptoms by bringing more lead into solution. The manner of action of this drug is still a subject of controversy. It seems, however, to be in all forms of lead poisoning the best eliminative available. The pains of lead colic should be controlled by hot applications, or, if severe, by warm baths, by the inhalation of amyl nitrite or by hypodermics of atropine or pilocarpine; vasomotor dilators have an instantaneous action in relieving pain. Morphine is to be avoided unless the pain is so extreme and uncontrollable that it must be used, since it interferes with the elimination of lead and of general metabolic products through the kidneys, and usually constipates. Oliver warmly recommends monosulphite of soda in doses of 5 grains (0.3 gm.) for both colic and paralysis in mild cases.

Paralysis should be treated by the general principles used in managing peripheral neuritis. Active treatment should be begun only when the acute progress of the palsy has ceased. The most important measures are electricity, carefully graduated massage with passive exercises, and, so far as possible, very slowly increased active exercise. The treatment must be long-continued, and if complete recovery does not occur it should not be stopped until all improvement has ceased for months. Since there is usually decided impairment of the general health in these cases, general treatment is almost as important as local. Moderate general exercise, provided the paralysis permits of it, as it nearly always does, should be used after preliminary rest in bed; fresh air, sunshine and a generous diet must be insisted upon at all times when they can be had. Bitter tonics are useful. Strychnia is not in as good repute as a cure for paralysis as it once was, but is an excellent general tonic and stomachic, and certainly will do no harm if used only after evidences of increase in the paralysis have clearly ceased. The usual anemia needs fresh air and food, especially; but small doses of arsenic ($\frac{1}{100}$ grain continued for only short periods, as arsenic also causes nerve-degeneration) will often improve both the anemia and general nutrition. Iron is not very effectual in such anemias, and if given should be used sparingly, lest it disturb digestion and increase constipation. The general measures mentioned are likely to be necessary in any case, whether paralysis is present or not, in order to secure recovery of good, general health.

Cerebral symptoms need to be managed with much care. There is so much danger of exhaustion that severe eliminative measures should not be used. The bowels must be kept moderately active, and diuresis should be stimulated by free water drinking. Convulsions or delirium should be treated with large dose of bromides, combined with hyoscine or chloral. Hot packs are sometimes useful. Morphine should not be used except as a last resort, and then with care, because of its interfering with elimination. Moderate venesection is a more suitable measure in actively severe cases than is generally taught; there is sufficient evidence of cerebral congestion to justify it in such cases. Good results have several times been obtained from lumbar puncture, and it is reasonable to use it if the cerebral symptoms are persistent and urgent; in several of Gibson's cases the finding of an excessive amount of fluid under a high degree of tension was recorded.

In both prophylaxis and treatment it is of the greatest importance to exclude alcohol absolutely.

CHRONIC ARSENIC POISONING

To the clinician chronic arsenic poisoning is of constant and rather especial interest because, unless somewhat cautious in the use of arsenic, he may see chronic poisoning as a result of his own administration of the drug; he is, indeed, much more likely at present to see poisoning from this source than from any other, unless he has an unusual situation in regard to occupations that cause exposure. The condition is of especial interest, because chronic sequels of acute poisoning occur not infrequently. Arsenical neuritis, for example, may result from a single dose taken by accident or in an attempt at suicide, and several more or less prolonged conditions due to lesions of the nervous system are now seen following the isolated injections of salvarsan.

Etiology.—Chronic arsenic poisoning, caused by various articles in domestic use, is quite familiar to the public at large. Wall paper in particular caused many cases of poisoning, and in Sweden still gives rise to many cases during the long winter housing. The observations of Gmelin in 1839 and of Basedow in 1846 caused the passing of a Prussian law forbidding the use of arsenic in dyeing paper. In this country it was not until many years later (in 1900) that a law was passed in Massachusetts, strictly limiting the amount of arsenic permissible in papers and articles of dress.

Arsenical poisoning, however, was caused by papers of various other kinds, such as those used for wrapping purposes, for making paper flowers and playing cards. It was seen as a result of the use of arsenical book covers, crayons, arsenical paint used for interior work, and numerous other objects of diverse kinds, particularly bed-room hangings and clothing of various sorts, stockings, hat bands, gloves, and dress goods of numerous kinds. There still is a wholly wrong impression that green is the chief or only color likely to be arsenical.

Foods were a frequent source of danger, but at present this source

has practically disappeared, though an extensive epidemic of arsenic poisoning among beer-drinking people in England occurred not long ago; the arsenic was derived from the sulphuric acid used in manufacturing the glucose employed in making beer.

The occupations that cause danger are more limited in number than they were. The chief dangerous occupations are the mining and smelting of arsenical compounds and of ores containing considerable quantities of arsenic, among the latter being particularly zinc, silver, and lead. Those engaged in working upon the skins of animals and birds, some hat makers, and dye makers, are also exposed to poisoning. In occupational poisoning, skin symptoms are the most common chronic results.

The chief sources of poisoning, however, are at present suicidal or accidental ingestion of toxic amounts of arsenic, or large or prolonged dosage for therapeutic purposes. The frequent use of salvarsan gives many instances of acute poisoning and some few cases in which late effects of a chronic type are seen. Poisoning from therapeutic use of arsenic has usually occurred in cases of skin disease, syphilis, chorea, pernicious anemia and other severe anemias, or Hodgkin's disease, in which conditions the drug is likely to be used for a long time and in large doses.

Pathology.—The lesions in chronic poisoning have not been extensively studied, as death is an unusual result of chronic poisoning. Even severe symptoms are usually recovered from, more or less completely. Skin lesions, anemia, and changes in the nervous system are most common. Gastro-enteritis, nephritis, and fatty change of the liver, vascular system, and muscles, are conspicuous in the acute poisoning, but much less so in the chronic form. Of the skin lesions, pigmentation is much the most interesting from the pathological as well as the clinical standpoint. It is due to a deposit, most marked in the lymphatics of the papillæ, of a pigment that is of somewhat uncertain origin; it has not been satisfactorily determined whether or not it is derived from hemoglobin.

The nervous lesions are in both the peripheral nerves and the spinal cord; arsenic produces chiefly degeneration and atrophy of the cells of the anterior horns, sometimes degeneration of the white matter. The peripheral nerves may show degeneration of the myelin and at times of the axis-cylinder.

Mode of Entrance and Pathogenesis.—The commonest mode of entrance is therapeutic, suicidal, or accidental administration by the mouth. Several general lesions may be produced by means of external application. Arsenic may also be inhaled as dust in some occupations, and the volatile compounds of arsenic are, of course, readily taken in by respiration. Chronic poisoning from wall paper proved to be of much interest in the latter regard. It was by many thought to be due to arsenical dust from the paper, but it was demonstrated that a volatile compound was formed. The volatile compound is apparently arseniuretted hydrogen, and is produced by a number of moulds, among which *Penicillium brevicaulis* is the most important.

The manner in which arsenic acts on entering the system is a subject

chiefly of speculation. In small doses it seems to stimulate the bone-marrow to blood-formation; in large doses it produces degeneration of the marrow and causes anemia. Very large doses set up general tissue destruction. Many of the local effects are due to excretion; this occurs chiefly through the kidneys, but also through the skin and various mucous membranes and glands, such as the liver and the breasts. Mother's milk has caused fatal poisoning of infants. Many instances of disease of the skin, conjunctiva, etc., are due to excretion.

Individual susceptibility plays a large part in determining the occurrence of poisoning. Less than a fluidounce of Fowler's solution taken over a period of a few weeks has caused severe intoxication; while large doses are definitely known to have been taken for therapeutic purposes for even thirty years or longer without ill effects, and arsenic eaters have apparently accustomed themselves to frequent doses of several grains, continued with impunity for very many years.

Symptoms.—Peripheral neuritis and skin lesions are the most important as well as the most common results, and not infrequently marked disease of the skin or nervous system occurs without other noteworthy disturbance of health. General symptoms are chiefly anemia, emaciation, persistent headache, general weakness, irregularity or weakness of the heart action, and vasomotor disturbance. There is also more or less disorder of the gastro-intestinal tract; occasionally evidences of chronic nephritis are present and at times a slight irregular fever, but one's attention is ordinarily directed chiefly to the skin or the nervous system.

The most striking skin symptoms are keratosis and pigmentation. *Keratosis* occurs chiefly on the palms and soles; it may be diffuse, or localized in small areas, and may be of any grade up to the most severe. Ordinarily marked desquamation takes place in connection with the keratosis and this may occur even in large scales or plates. The localized horny areas have some tendency to become epitheliomatous. *Pigmentation* is extremely important clinically. It has repeatedly been mistaken for other forms of pigmentation, such as that of Addison's disease. It varies in intensity from a slight yellowish-brown tint to a deep brown, and it may be diffused over the whole surface, when it is usually of moderate or slight degree; or, more frequently, it is collected in local areas, particularly on exposed surfaces, or in the folds of the joints, as the axilla, regions exposed to pressure, or in parts, such as the nipples, that are normally pigmented. Sometimes small spots of pigmentation may occur, somewhat resembling moles. The mucous membranes may show pigmentation. Deep pigmentation may be present in local areas, together with a higher degree of diffuse discoloration. As a rule, the pigment slowly disappears after cessation of the poisoning, but it may remain permanently, to a greater or less degree.

A variety of other lesions of the skin also occur. Erythema, papular, vesicular, and bullous eruptions, pustules and boils, are common, as are thickening, brittleness, and roughness of the nails, loss of hair, occasionally urticarial, psoriasis-like, and other eruptions. Glossiness of the skin and herpes have been seen, at times in association with neuritis; the hyperhidrosis with maceration of the skin of palms and soles and the

erythromelalgia-like condition of the feet depicted by Kelynack and Kirby are probably due to vasomotor changes.

Among the manifestations suggestive in diagnosis is the condition of the exterior of the eyes. There is often puffiness of the eyelids; the conjunctiva is congested and frequently somewhat swollen; there may be marked chemosis and running from the eyes.

Of the symptoms referable to the nervous system, *paralysis* is much the most important, though considerable variation may be seen. These symptoms are nearly always the result of internal use of arsenic. Paralysis following a large toxic dose appears a week or ten days, or even later, after the poisoning, when the acute symptoms due to disturbance of the gastro-intestinal tract and other direct irritative symptoms have more or less subsided. In chronic poisoning the time of appearance of paralysis depends, of course, upon the dose, and upon individual susceptibility. Paralysis is usually preceded by disturbances of sensation; paresthesias are very common, pain is strikingly frequent and extremely distressing, both before the paralysis appears and for some time after it has developed; its frequency and severity constitute important indications of arsenic poisoning. The nerve trunks, also, are frequently sensitive to pressure, and the skin may be extremely hyperalgesic upon touch or pressure. With the progress of the palsy, all qualities of skin sensation become reduced or lost.

Motor palsy usually develops subacutely in cases which follow acute poisoning; in rare instances it appears very suddenly. It may, however, develop slowly even when due to acute poisoning, and in chronic poisoning this is generally the case. Like the anesthesia, it is most marked and most common in the legs. The motor and the sensory palsy alike affect the distal portions of the extremities, and very rarely extend above the knees and elbows; while the upper arms, the thighs, the trunk muscles, and the sphincters escape. Both the extensors and flexors are involved, and there is no tendency to spare certain muscles as in lead palsy, all muscles of the areas affected suffering. The extensors are, however, usually more severely diseased than the flexors. It is very unusual for the arms to be affected without the legs, and paralysis localized to one extremity is rare, though it has occurred. Typical cases of polyneuritis are reported by von Jaksch. The knee-jerks are almost always lost when palsy is at all marked. Degeneration reactions are present, and the response to faradism is reduced or lost. Atrophy develops within a few weeks and often becomes extremely marked. Contractures of much severity are frequent when well-developed poisoning has been present for some time.

Cases of rapidly fatal progress are almost unknown, but the disability that develops may be extreme and death may occur with the appearance of general cachexia. Unless, however, the paralysis is very severe or has been long neglected, improvement usually begins after a few months at most, and it progresses in most cases to complete or almost complete recovery, though occasionally marked disability may persist.

Since the introduction of salvarsan there are more instances in which single cranial nerves have been affected; the auditory and the

optic nerve appear to suffer chiefly; ptosis has occurred and other external eye muscles have been paralyzed. Lagophthalmos has been described. Amblyopia and amaurosis occasionally appear. Cloudiness of the lens has been reported after acute poisoning, and is said to occur as a result of chronic poisoning. Aphonia from laryngeal paralysis has been reported.

There is an interesting and important group of cases to which attention was directed by Dana,¹ in which ataxia, particularly of the legs, is so conspicuous a feature that it may readily lead to a diagnosis of tabes dorsalis, unless the mode of onset, the presence of neuritis, and the absence of involvement of the sphincters are carefully noted. Psychic symptoms sometimes occur.

Diagnosis.—Headache, skin lesions, darkening and thickening of areas of the skin, puffiness or watering of the eyes, catarrhal symptoms in the nose and deeper respiratory tract, gastro-enteric irritability, or painful extremities, in a patient taking arsenic or in an arsenic worker, should at once put us on our guard against further exposure to poisoning; peripheral paralysis with sensory disturbances following in the wake of these symptoms is doubly suggestive.

The paralysis may have to be distinguished from lead palsy, alcoholic neuritis, and neuritis due to various infections and other causes. Lead palsy is usually readily excluded by the severe pains and other sensory disturbances, by the more marked involvement of the legs than the arms; by the absence of a history of colic, by the absence of cachexia and a blue line on the gums, and by the escape of the supinator muscles from the paralysis affecting the forearms. The other conditions will be excluded, as a rule, only by finding a source of arsenic or by searching for arsenic in the urine. If peripheral palsy appears in a person who has no history of alcoholism or infection, associated with severe pains in the particular nerves, and the other characteristics of arsenical paralysis, a source of arsenic should be carefully searched for, and the urine should be examined for it.

Cases due to arsenical wall paper, carpets, dress goods, etc., are not very rare; the diagnosis will depend solely upon chemical investigation of suspicious objects and of the urine. In this class the symptoms have often been obscure, and if so, whatever the source of the arsenic, the diagnosis is likely to be suspected only in case there is a careful consideration and search for all possible causes of the disorder.

Prognosis.—General symptoms usually disappear gradually if properly treated; and, if the poisoning ceases, the skin disorders are usually recovered from, though often slowly. Keratosis or ulcers occasionally become epitheliomatous. Pigmentation greatly improves or disappears, though at times remains permanently. The nervous symptoms are, in general, of good prognosis; like all toxic paralyzes, however, those due to arsenic are occasionally permanent, or show little improvement if they have reached a severe grade, and especially if treatment is long delayed. Marked psychic symptoms are unusual.

¹ Brain, 1886-87, ix.

Prophylaxis and Treatment.—The prophylaxis of industrial poisoning should follow the principles discussed under lead poisoning. When these are properly used they prevent a very large proportion of the evil results. Intoxication from the therapeutic use of arsenic can usually be avoided by care in administration.

The treatment must be regulated according to the conditions to be cared for. Potassium iodide in moderate doses, 5 grains (0.3 gm.) after meals, is generally considered a useful eliminant, but there is no specific treatment. Skin lesions should be managed in accordance with the individual case, and paralysis should be treated as multiple neuritis is treated. In the earlier stages of the latter, pain will frequently be a troublesome feature, and will require symptomatic treatment. Rest is essential until all irritative symptoms are past. Carefully graduated massage, electricity, and passive movements, with slowly increased active exercise, must be used persistently. Avoidance of alcohol and careful regulation of the hygiene of life are to be insisted upon.

CHRONIC MERCURY POISONING

Besides causing ptyalism, mercury may cause a chronic poisoning with a well-marked group of symptoms and a so-called late or delayed poisoning which is of special interest.

Etiology.—The importance of chronic mercurial poisoning has decreased in recent years, partly because much greater care is now exercised in using mercury medicinally, but much more because in a number of industries in which mercury poisoning was once common, this metal is not now used, or the industries themselves have given way to others that accomplish the same purpose. The chief industries in which this poisoning is now seen are mercury mining and smelting, the manufacture of thermometers, barometers, and other physical apparatus of which mercury is an essential part, and the manufacture of felt hats, the acid nitrate of mercury being used in the latter in treating the felt. Chronic mercurialism also occurs among men engaged in the production of various salts of mercury in chemical plants, though to what extent is difficult to determine. Salivation is not uncommon among them and chronic poisoning must occur occasionally, but it is probably quite rare.

Poisoning from the medicinal use of mercury occurred not infrequently until the danger became thoroughly and generally recognized. At present, chronic mercurial poisoning from this source is extremely rare. It is almost always preceded by more or less ptyalism.

Pathology.—Wising has described degeneration and atrophy of the myelin in the lateral columns of the cord and reduction in the number of fibres, and Brauer has noted, experimentally, degenerative changes in the cells of the anterior horns, using the Nissl stain. Alensi and Pieri found extensive alterations in the ganglion cells of the cerebral cortex. Prolonged medicinal use, and sometimes occupational poisoning, may cause anemia and marked emaciation, with fatty degeneration in various organs, and chronic gastro-enterocolitis. Both von Jaksch and Kobert

consider a cirrhotic kidney as a common condition in chronic poisoning and a mercurial necrosis of the jaw is described.

Mode of Entrance.—Mercury may enter the system by inhalation as a vapor, and it is probably the chief way in which occupational poisoning occurs, though absorption through the skin seems to play a rôle of considerable importance. In the manufacture of hats, the preparation of skins, and similar processes in which much dust is created, inhalation of actual particles occurs. There are always ready opportunities for inhalation poisoning when mercury itself is used, since it volatilizes at ordinary temperatures, and furthermore the heating processes necessary in most of these industries largely increase the volatilization. Frequent ingestion of small particles is probably a factor of much importance in occupational poisoning.

Symptoms.—It is a striking fact that salivation and stomatitis are very often absent in the chronic cases. The gums and teeth are usually found in fairly good condition, save that, as is often the case in mercury workers, the teeth show blackish discoloration and a black line on the gums is spoken of; von Jaksch speaks of a mercurial necrosis of the jaw. At times persistent pyalism does develop, generally before the nervous symptoms. In the early stages of poisoning and when the condition is more pronounced, the patients often complain of headache, restless sleep, and marked depression and weakness, particularly in the morning. Sometimes anemia develops and, in severe cases, a condition of general cachexia appears. Gastro-intestinal disturbance is not uncommon. Neuralgic pains, especially in the territory of the trigeminus, are quite common in both early and advanced stages, and joint pains also occur. Loss of sexual power has been noted.

The most striking and common features of chronic mercurial poisoning are *tremor* and a peculiar *emotional disturbance* or *erythism*. These are usually associated with each other in greater or less degree from the beginning. The tremor in early stages is absent when the subject is quiet but appears upon voluntary effort, especially upon finely coördinated movement, such as writing. Emotional influences usually have an intense effect in increasing the tremor, bringing it out when not otherwise present. It may be slight and of small amplitude, but is more likely to be a rapid, gross movement, and is frequently so severe that it at once makes legible writing wholly impossible. After a few moments the tremor and excitement decrease and within a short time they have nearly or quite vanished. The hands and lips are chiefly affected; if the condition is marked, however, most of the facial muscles are involved and all the extremities may show tremor. All grades of severity may be seen, and the phenomenon in severe cases is most remarkable.

Physical examination, even in marked cases, usually shows nothing beyond the tremor except, perhaps, slight or moderate muscular weakness. Occasionally weakness is very marked even when other symptoms are absent. Nystagmus has been described but is very rare. The speech is frequently much disturbed by the severe tremor of the lips and facial muscles. Choreiform movements, anesthesia, and irregularly distributed paralysis may occur.

The emotional disturbance or mercurial erythism is closely associated as a rule with the tremor. Sometimes, however, it is very marked when the tremor is but little existent. Most of the patients notice this emotional disturbance before anything else, and may further complain of symptoms most characteristic of the severer grades of neurasthenia, psychasthenia, and hysteria; very rarely do they show an actual psychosis.

Convulsive attacks are described. Two types of convulsions have been attributed directly to mercury. In one of them the convulsive action is tonic and follows violent movements or hard work, and affects chiefly the flexors of the forearm. In the other type the convulsions are clonic. These occur in violent paroxysms, there is marked oscillation of the head with movements of the eyelids and eyeballs, the facial muscles, and the arms and legs. The attacks are often painful, but there is no loss of consciousness.

In addition to the disorders mentioned, neuritis has been described. Leyden discussed it in 1893. A few cases have been described in which there was severe ataxia. Kussmaul has described aphonia from laryngeal paralysis. There may be exaggeration of the special senses, as hyperacusis. Shivering feelings and sensations of cold are common.

The late or delayed mercury poisoning is seen in subjects who have apparently recovered from the primary irritative effects of the ingestion of large doses of mercury, usually the bichloride; after the first day or two of gastro-intestinal distress, follows a short period of comparative well-being, in which diminution of the amount of urine secreted may be the only suspicious symptom. Later albuminuria and the signs of acute parenchymatous nephritis appear; absolute anuria occurs in many cases, lasting at times six or seven days, and the victim dies in from ten to fourteen days after the fatal dose. A distressing clearness of mind may be present almost to the end. Uremia closes the scene; acute parenchymatous inflammation of the kidneys is the chief lesion found. Recovery has taken place from doses as large as eight and ten grains of the bichloride.

Diagnosis.—The chief conditions that are likely to cause confusion are disseminated sclerosis, alcoholism, and lead poisoning. The nature of the occupation and the knowledge and determination of the fact that mercury is used, if necessary the demonstration that mercury is present in the urine, are important points. The wide amplitude and irregularity of the movements, the remarkable effect of emotional influences, the absence of nystagmus and of any evidence of focal cerebrospinal lesions, and the strikingly tremulous and emotional character of the stammering, distinguish the condition from *multiple sclerosis*. Frequently *alcoholism* is actually associated with mercurial poisoning; in such cases the very severe tremor, the peculiar erythism, and the extremely marked influence of the latter upon the tremor should suggest poisoning by mercury as well as alcohol. When alcoholism is not present it may be excluded by the history and by the absence of all signs of it except tremor and excitability, and the last-mentioned features differ in the two conditions. *Lead poisoning* will almost always be indicated by the occupation, by attacks of colic, and by a blue line rather than a black.

Prognosis.—If the tremor has not become constant and there is no marked cachexia, recovery practically always occurs under proper surroundings. Even severe and persistent tremor usually disappears ultimately, as does the emotional disturbance. If there is paralysis, mental disturbance, advanced kidney changes, or severe cachexia, the outcome is doubtful. Sometimes even moderate tremor never wholly disappears, and in any instance recovery is likely to be very slow. Prognosis depends largely upon freedom from further exposure.

Prophylaxis and Treatment.—As in almost all similar conditions, the majority of cases of poisoning can be prevented if employers properly protect their workmen. The results of the energetic and successful efforts of Wollner in enforcing proper hygiene in the mirror factories at Furth are profoundly impressive in this regard. Thorough ventilation is the most essential point, as is shown by Wollner's experience. Cement floors and other forms of construction that permit of thorough cleanliness and prevent the accumulation of particles of mercury, the use of hoods whenever possible and of well-covered containers for the mercury, with the requirements that the employees cleanse their hands before eating, cleanse their persons thoroughly, and protect their hands with rubber gloves while at dangerous work, are also of the greatest importance. Free and nutritious diet, abstention from alcohol and from sexual and other excesses, with a generous amount of exercise in the open air are of the utmost value in prophylaxis and treatment. Many workmen take small doses of potassium iodide at frequent intervals as a prophylactic, particularly if they have already had slight symptoms, and a number have recovered from marked poisoning without cessation of work by treating themselves in the manner indicated. Turkish baths and frequent hot baths are also useful.

The measures mentioned are the most important in any stage of poisoning, as well as in prophylaxis. Sometimes the severity of special symptoms, particularly the tremor, may demand medicinal treatment. Sedatives such as derivatives of opium, chloral, bromides, and also belladonna and pilocarpine have been found useful.

PHOSPHORUS POISONING

The history of phosphorus poisoning practically begins with the invention of phosphorus matches in 1833. A little more than a decade later the descriptions of Lorinser, Heyfelder, Strohl, and particularly of v. Bibra and Geist, of the distressing effects of phosphorus upon workers in match factories, aroused most intense interest. Since then a number of European countries have forbidden the use of poisonous white or yellow phosphorus in making matches, and, as a consequence, non-poisonous matches are now made in enormous and increasing quantities in these and other countries. Acute poisoning is still common in a few countries, such as Sweden, and phosphorus necrosis still occurs with some frequency in a small number of European countries in which workmen have little or no legal protection and the hygienic conditions are poor.

Etiology.—Industrial (chronic) poisoning has usually occurred in the manufacture of phosphorus itself, but is almost always due to the much more dangerous exposure that occurs in the use of the crystalline white or yellow phosphorus in making matches. Phosphorus volatilizes at room temperature, and in dipping and packing the matches, exposure to the vapor inevitably occurs unless the work-rooms are large, extremely well-ventilated, and kept scrupulously clean.

“White” phosphorus, which becomes “yellow” phosphorus on exposure to light, forms amorphous “red” phosphorus if subjected to a high temperature in an atmosphere free of oxygen. This red phosphorus, which is used in making most safety matches, is almost harmless to those working with it, even if swallowed. Accidental chronic poisoning has been reported in rare instances. Acute poisoning is due, as a rule, to attempts at suicide, generally by swallowing match heads; twenty-five match heads usually contain enough phosphorus to cause grave or even fatal poisoning of an adult.

Pathology.—Experimental chronic poisoning has produced hepatic cirrhosis and chronic interstitial nephritis. The result of chronic poisoning in human subjects is almost always necrosis of the jaw with subsequent sequestrum formation and suppuration of the bone and the nearby tissues, the lesions being very extensive in cases not treated early. General fragility of the bones has been described.

The changes in acute poisoning are reduction or loss of coagulability of the blood, diffusely scattered small or larger hemorrhages, areas of gangrene from emboli of fat, icterus, loss of elasticity of the vessels, fatty changes in the muscles, heart, kidneys, stomach, and duodenum, enlargement of the spleen, and very extensive changes in the liver; the latter organ is enlarged, of saffron color, a typical fatty icteric liver, the acini, large and easily seen, and microscopically there is an extensive deposit of fat; some of the liver cells are merely filled with fat, others are undergoing destruction or have been entirely destroyed.

Intermediate products of metabolism in abnormal amounts or substances that are entirely abnormal—leucin, tyrosin, cystin, sarcosolactic acid and peptone-like or ptomaine-like substances—are found in the blood and urine; glycosuria often occurs; there is very excessive acid production and the power of oxidizing acids is reduced. As a consequence, the ammonia of the urine is greatly increased while the urea is diminished. The last-mentioned conditions are due chiefly to the acid intoxication, not to the loss of the liver's function of producing urea.

Symptoms.—Acute poisoning bears a very close resemblance to “idiopathic” icterus gravis and acute yellow atrophy. Some hours after taking phosphorus, vomiting and often diarrhœa appear; the vomitus may have the odor of phosphorus. The symptoms remit after the digestive tract is emptied, and for two or three days the patient seems almost or quite well. After this, vomiting returns and icterus develops, also epigastric pains, tenderness of the whole trunk, and distressing pains in the muscles, which are probably in large part the result of hemorrhage into the tissues. There may be fever. Blood is often present in the vomit and stools, and petechiæ occur in the skin and

mucous membranes. The liver enlarges a day or two after the return of the symptoms and grows tender; later it may decrease in size, but usually it does not unless recovery occurs. The patient becomes apprehensive, sleepless, and prostrated; in some instances, marked somnolence, coma, or maniacal excitement appears a day or two before death. The urine, when poisoning is well developed, contains much sarcolactic acid, at times leucin, cystin, occasionally tyrosin. The ammonia of the urine is greatly increased, the urea is diminished; the total nitrogen excretion is ordinarily increased beyond the intake.

In fatal cases, the end generally occurs after about a week, sometimes earlier. Fully half the cases die. If recovery takes place the symptoms gradually subside, the liver decreases in size, and it may ultimately shrink to less than its normal dimensions: a polycythemia may be found. There may be sequelæ such as neuritis and paralysis from cerebral hemorrhage. Death after subsidence of acute symptoms may take place from fatty degeneration of the heart muscle.

Chronic poisoning consists almost entirely of necrosis of the jaw and neighboring tissues, and the consequences of this local disease. General disturbance of health without necrosis is described by some observers, as well as recurrent attacks of acute bronchial catarrh with œdema of the lungs. Necrosis occurs particularly in those whose mouths and teeth are in bad condition from the effects of phosphorus, plus those of bacterial action, and conditions that favor bacterial growth favor necrosis. It begins usually about a single tooth, most commonly in the lower jaw, with local decay and abscess formation. If not treated quickly, the disease spreads and the gums become loosened. If the tooth is removed, exceedingly foul pus is discharged from the alveolus, the necrosis advances to neighboring teeth and to further portions of the jaw-bone, sequestra form, the suppuration extends to neighboring tissues, sometimes burrowing deeply into the neck, frequently breaking through the skin; the patient becomes weak and anemic and is likely to develop amyloid disease, pulmonary tuberculosis, basal meningitis, or general septicemia. Occasionally other bones of the head, contiguous to those of the jaw, become necrotic. General fragility of the bones believed to be due to chronic phosphorus poisoning has been seen. It has been repeatedly observed that necrosis may make its first appearance two or three years after the subject has ceased working in phosphorus. If local treatment is instituted very early the necrosis is sometimes controlled without serious surgical measures.

Diagnosis.—Acute poisoning is distinguished from acute yellow atrophy chiefly by the history of poisoning; by the appearance of jaundice and other severe symptoms two or three days after temporary gastric symptoms, while in acute yellow atrophy, the grave symptoms are usually preceded for some time by signs of catarrhal or obstructive jaundice; by the enlargement of the liver; by the fact that leucin, and more particularly tyrosin, are less common and less abundant than in acute yellow atrophy. Cerebral symptoms are also much less frequent. Phosphorus necrosis is diagnosed chiefly by means of the occupational history, with persistent and advancing necrosis of the jaw.

Prognosis.—Acute poisoning is always very grave, one-half or more of the cases ending in death. The prognosis depends largely upon the promptness with which the stomach is emptied and further treatment instituted. If severe symptoms develop, it depends upon their duration; with each day beyond three or four that such symptoms continue, the outlook grows much more grave. The course of necrosis depends upon the rapidity and thoroughness of treatment. Early resection is usually successful. Advanced disease and long-postponed treatment render the prospects doubtful as to recovery, and, at best, the disfigurement is likely to be severe.

Prophylaxis and Treatment.—Phosphorus necrosis would practically disappear were the use of white phosphorus in making matches everywhere forbidden. Constant and thorough care of employees' mouths and teeth, attention to the hygienic conditions in the work-rooms, with the use, whenever possible, of machinery in place of handwork, would almost entirely prevent serious results.

The treatment of the necrosis consists in removing the subject from danger upon the development of the slightest signs of necrosis, immediate dental treatment of the local disease, and, if it does not yield or in spite of this advances, early resection of the jaw. Acute poisoning should be treated by the immediate administration of copper sulphate, both for its emetic effect and because it prevents much of the absorption. The stomach should be washed out, using potassium permanganate solution (2 to 3 per cent.) or hydrogen peroxide (1 to 3 per cent.) for their oxidative action, since the oxides of phosphorus are little, if at all, poisonous. A purge should be given, avoiding castor oil, since oils and fats (milk) increase the solution of phosphorus. Old, ozonized turpentine should be given in doses of 0.5 cc. (Mvii) three or four times daily for a week or more, as it is supposed to favor oxidation of the phosphorus. Alkalies should be administered. If there are severe symptoms, the dose of alkali should be very large in order to combat the acid intoxication, and intravenous administration of alkalies may be used as in diabetic coma.

CHRONIC SILVER POISONING OR ARGYRIA

Argyria is of two forms, local and general. The former occurs in those who handle silver in their occupations, when it is seen chiefly in the skin of the hands, a condition first described by Lewin.¹ It may be due to prolonged use of silver preparations, particularly in hair dyes, or in treating diseased mucous membranes of the eye, throat, and other parts; de Schweinitz² and others have directed attention to the danger accompanying long-continued use in this way of the newer silver preparations, such as protargol.

General argyria has also occurred in a few instances from prolonged occupational contact with silver, and, in a smaller number of cases,

¹ *Berl. klin. Woch.*, 1886, p. 17

² *Transactions of the American Ophthalmological Society*, 1903.

from its protracted local application. In a great majority of instances, however, argyria has been due to the therapeutic internal use of silver nitrate. In slight degree the condition has been set up by as little as 2 grams (30 grains) administered in the course of two months; but when marked general discoloration occurred, the amount has generally been much larger, 15 grams (3 ss) or more. The comparatively frequent occurrence of argyria in earlier times, and the very unfortunate results, led to such general and emphatic warnings against the possible production of it that the condition has become quite uncommon.

Pathology.—Argyria consists of a deposit of silver in the skin or mucous membranes alone in the local form, in the internal organs also in the general form. In argyria due to internal use of silver, the pigment is found in the papillæ of the skin and in the glands, but not in the epithelium; in occupational cases, in which it enters from the exterior, it may be found in the epidermis. In generalized argyria most of the organs may show pigmentation, but it is ordinarily most marked in the kidneys, liver, and choroid plexus. The pigment is situated in the vessel walls and the nearby tissues. In the early stages it is first found in the leukocytes. Silver salts, when absorbed, form an albuminate, and this is gradually deposited and reduced.

Chronic interstitial changes in the liver, lungs, and kidneys have been described as a result of the prolonged presence of the pigment in the tissues.

Symptoms.—The condition consists of a more or less disfiguring pigmentation without any subjective symptoms; an isolated case of neuritis with symptoms resembling the forearm-extensor palsy of lead poisoning is mentioned by Gowers. Marked mental depression and abnormal shyness may naturally result from the very marked disfigurement. As a rule, however, pigmentation is the sole result. When this is due to local application or to occupation, the discoloration begins in the areas that come directly in contact with the silver, and in such it usually remains localized. If it results from internal use of silver, the first pigmentation is almost always seen in the form of a line on the edge of the gum that resembles the lead line, but is of a more violet color. This line is of diagnostic importance and also serves as an important warning, since it appears well before the pigmentation of the skin, and indicates the necessity of stopping the use of silver at once. When skin pigmentation develops from internal use, it is at first in patches, chiefly in areas much exposed to light; the patches afterward coalesce and the whole surface—skin, conjunctiva, and other visible mucous membranes—ultimately shows more or less pigmentation. Slight grades resemble moderate degrees of cyanosis; in more severe cases there is a very striking and characteristic slate-gray color that makes the appearance of the individual extremely conspicuous. If distinct pigmentation is allowed to develop while silver is still being administered, the discoloration usually grows more marked after the drug is discontinued, because a considerable amount of unreduced silver is always present in the body under such circumstances, and reduction goes on for some time. The color may indeed continue to deepen slightly for

many months; in one case, it apparently continued to grow darker for years. The color sometimes varies greatly on bright and dark days.

Diagnosis.—The discoloration may be mistaken for cyanosis, and the line on the gums may be confused with the lead line. The nature of the condition is determined by the history, or, if desirable, by excising small portions of skin and finding that in sections the pigment granules disappear after treating with potassium cyanide or concentrated nitric acid, and reappear upon adding ammonium sulphide. There is no practically likelihood of mistaking the condition for anything else when the color has once been seen and recognized.

Prognosis.—Once developed, the pigmentation is permanent. If there is merely a line on the gums, disfigurement of the skin may usually be avoided by discontinuing the use of silver at once. If the skin already shows discoloration, this generally deepens somewhat, even if the drug is stopped.

Prophylaxis and Treatment.—The prophylaxis consists in the exercise of great care in prescribing silver nitrate, not giving more than one-fourth grain doses and not continuing it for more than six weeks. If it is desired to use the drug further in the same patient, there should then be an intermission of several weeks. Patients should not be given solutions of silver to use without the supervision of a physician, and they should be warned against the danger of having prescriptions refilled for internal use or external application.

There is no treatment for argyria, all practicable methods of combating the pigmentation being entirely unsuccessful.

CHRONIC ZINC, COPPER, BRASS, TIN, AND MANGANESE POISONING

How many of these substances produce chronic systemic disease is an unsettled question. There is little doubt that most of them may produce digestive disturbance; and the presence of zinc, copper, or tin in preserved foods should therefore be considered prejudicial to health. There is likewise no doubt that the respiratory tract may be damaged by inhalation of dust in the manufacture of any products of these metals. Chronic systemic effects have, however, been but rarely observed, and, except as regards *zinc*, it has never been clearly shown that the systemic effects described were not due to other unquestionable systemic poisons, particularly lead and arsenic, that are known to be frequently present in the metals under discussion, or to sulphurous and sulphuric acid, carbon monoxide, and other fumes that are given off in the heating of these metals. Kobert has found that zinc workers often excrete large amounts of zinc for months without any evidence of poisoning, but the condition spoken of as "brass workers' ague," "zinc chills," is very probably produced by the inhalation of the zinc oxide fumes and dust.¹ Zinc chloride may produce severe skin irritation through external action.

¹ Hayhurst, *Amer. Jour. Med. Sc.*, 1913, cxlv, 723; von Jaksch, *Vergiftungen*, 1910.

Brass workers are a shockingly short-lived lot and suffer from gastrointestinal diseases, anemia, and chronic lung diseases.

No evidence of poisoning by *copper* has been found in the employees of the great copper companies in Michigan or in the people who live in the regions about the mines and who drink water that often contains copper. Similar observations have been made by many other writers. Soluble copper salts apparently do not cause chronic poisoning. Copper is known to produce some disfigurement through greenish discoloration of the teeth, the hair, and occasionally the skin of the face and other parts. Even a green color of the sweat may be seen.

The cases of tin poisoning that have been described were probably in most instances intoxication from decomposed canned foods. There are no cases on record that were clearly instances of chronic tin poisoning.

There are no diagnostic signs of any of the poisonings under discussion, as they are not positively known to occur. In cases in which these metals were suspected of producing poisoning, the prognosis seems to have been much like that in lead poisoning; and the treatment should follow the same principles.

Chronic *manganese* poisoning is mentioned separately because it seems to possess some semblance of a distinct clinical picture. Embden, and later von Jaksch, describe a series of cases in which there was œdema, general weakness or pareses without atrophy or degeneration reaction, a mask-like appearance of the face, disturbance of speech and of the voice, gross tremor of the head and extremities much increased upon intentional movement, excited patellar reflexes and a spastic gait. The Romberg sign was absent. There were paresthesias and pains in the earlier stages but no other sensory symptoms. Sometimes there was uncontrollable laughter or weeping, and other psychic alterations were observed.

CHAPTER X

I. CARBON MONOXIDE POISONING. ILLUMINATING GAS POISONING. COMBUSTION PRODUCTS POISONING II. CHRONIC CARBON BISULPHIDE POISONING. POISONING BY THE FUMES OF NITRIC OXIDE

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I. CHRONIC MONOXIDE POISONING

WHILE various gases other than carbon monoxide are present in illuminating gas and in combustion products, and while it has been shown both experimentally and clinically that the effects produced by illuminating gas and combustion products are not wholly the same as those due to pure carbon monoxide, yet neither the clinical nor the experimental effects of the other gases that are present are sufficiently distinctive to permit of separate description of the three conditions.

Etiology.—Pure carbon monoxide poisoning has been excessively rare because opportunities for its occurrence have been most unusual. It has been seen in a few instances in laboratories. In recent years, monoxide poisoning has been seen as a result of careless manipulation of electric furnaces, and in chemical researches.

Intoxication with illuminating gas is commonly looked upon as being practically carbon monoxide poisoning, and carbon monoxide is certainly the chief agent in the poisoning. Water gas, as is well known, is particularly dangerous because of the large amount of carbon monoxide that it contains. Acute cases of gas poisoning are usually due to leaving the gas turned on in sleeping rooms, either by accident or in an attempt at suicide. Intoxication with illuminating gas sometimes occurs in the acute or chronic form in employees of gas works; and protracted poisonings of slight degree, occasionally acute and even fatal cases, may occur in the occupants of buildings into which gas escapes from leaks in the pipes or fixtures. The leak need not be in the building itself; the gas may travel through the ground for some distance, certainly for many yards, and hence while escaping from the mains may reach the interior of houses that are at a considerable distance from the break. Under these circumstances the odor of the gas is usually lost, and its presence may be detected only through the occurrence of poisoning. The exact frequency and importance of chronic illuminating gas poisoning is not well known, and it is hard to determine because of technical difficulties in the study of the question.

Combustion products cause poisoning chiefly as a result of the carbon monoxide they contain, though this is intensified by the other gases present, more particularly carbon dioxide. The amount of carbon monoxide in such gases naturally varies greatly, but it may be exceedingly large. In iron furnaces, for example, the escaping gas may contain as much as 25 to 30 per cent. Mild grades of combustion product poisoning very frequently occur and severe cases are not extremely uncommon. Nearly everyone has experienced transitory effects from gases produced by heating apparatus with poor draughts, and such mild effects are common in persons who are closely confined in rooms heated by badly drawing stoves or house furnaces. More or less severe effects also occur at times in cooks, and in persons employed in charcoal furnaces, iron and other furnaces, in coke ovens, in gas plants, in tar distilleries, in the moulding of various metals, and in kilns of various kinds (brick, tile, pottery, etc.). The "miners' disease" that has aroused so much interest has been shown to be due chiefly to carbon monoxide derived principally from the explosive used in blasting. Carbon monoxide poisoning also occurs at times in the employees of chemical factories. In the various occupations mentioned, severe and even fatal acute poisoning is sometimes seen, and chronic ill health occurs not infrequently.

The cases that occur accidentally in households are usually mild. Fatal cases have occasionally occurred even from modern heating appliances; in some European places, this is considered of such importance that the use of dampers in stove pipes is not permitted. When charcoal braziers and other fires without chimney connections were much used, domestic poisoning of all grades of severity was quite common. The common use of gas or oil stoves in small and ill-ventilated rooms has led to a noteworthy number of poisonings.

Pathology.—In acute cases, the striking features are the red or bluish-red spots on the surface of the body, chiefly the front of the neck, trunk, and thighs; the brilliant cherry-red color of the blood and of many or all the organs; the marked degenerative changes in the muscles; the scattered small hemorrhages and intense hyperemia of all the organs; and in many cases marked cerebral changes. Among the immediate or more remote sequelæ are gastro-enteritis, sometimes pseudomembrane formation on the upper digestive and respiratory passages, bronchitis, bronchopneumonia, or at times lobar pneumonia. Nephritis is common, sometimes with very severe degenerative changes and interstitial reaction. Peripheral neuritis has repeatedly been described, and poliomyelitis and disseminated encephalomyelitis have been seen. The most important nervous lesions, however, are those in the brain: they are chiefly hyperemic and small, scattered hemorrhages.

In chronic poisoning Koren has described fatty changes in the vessels and heart, with cardiac dilatation, anemia, splenic enlargement, and pleural effusions.

Mode of Entrance and Pathogenesis.—Carbon monoxide enters the system solely by inspiration, unless experimentally introduced otherwise. Its chief effect is in displacing the oxygen from oxyhemoglobin and

forming carbon monoxide hemoglobin, thus rendering the affected portion of the red-blood corpuscles incapable of performing their function as oxygen and carbon-dioxide carriers. This combination is a relatively fixed one. Oxygen cannot directly displace the carbon monoxide from its hemoglobin combination, and it is not probable even that any noteworthy amount of the carbon monoxide thus combined is oxidized to carbon dioxide and excreted in this way; but it has been established that dissociation of carbon monoxide hemoglobin occurs, and also that carbon monoxide is excreted as such, in the expired air, after poisoning. Detoxication is, therefore, always carried out to some degree and small, repeated doses are probably rapidly excreted in this way. An atmosphere becomes dangerous when it contains 0.05 per cent. of carbon monoxide (Gruber, Haldane). Severe symptoms may be caused by 0.02 per cent. (Haldane).

It is not yet fully settled whether the gas has any direct toxic action upon animal tissues or whether it acts solely by robbing the blood of its effective hemoglobin; a number of experimenters consider with much reason that it has a direct toxic effect upon the central nervous system, the muscles, the nervous mechanism of the heart, the peripheral nerves, and the parenchyma of various organs.

Symptoms.—The main symptoms of *acute* poisoning are an indefinite feeling of illness, usually accompanied by throbbing of the vessels, a burning sensation in the face, and soon severe headache, vertigo, and very marked muscular weakness, the latter being a somewhat characteristic and peculiar symptom. Nausea and vomiting often occur. If the amount of gas inhaled is large, severe symptoms develop; the subject becomes drowsy and then loses consciousness, and with this there is usually loss of control over the sphincters. Unconsciousness, as a rule, comes gradually, but sometimes, as with miners, it may be the first symptom, and the victim may drop suddenly. Muscular twitching is common, even in the earlier stages, and sometimes convulsions occur when the symptoms have become more marked. Very commonly the patient is not seen until he is unconscious, when he shows heavy and unduly rapid breathing, the pulse is sometimes fairly full and strong, but generally very rapid, and it is weak if the poisoning is severe or advanced. The skin and mucous membranes are usually more or less cyanotic, but this is sometimes made obscure by a peculiar and characteristic redness of the skin. There are, at times, the red patches on the skin mentioned under pathology. Drawn blood is bright, cherry red in color, and gives the characteristic reactions for carbon monoxide. If recovery occurs, there is a gradual awakening, and for some hours, often much longer, a hazy mental state persists. Coma may last many days and then be followed by recovery.

The sequelæ of some of the acute poisonings are common and interesting. There may be nothing but weakness and fever which may last for several weeks, particularly when pulmonary sequelæ develop. At times no cause for the fever is evident. The pulmonary sequelæ are bronchitis, bronchopneumonia, rarely lobar pneumonia, and are of extremely variable duration, sometimes causing death weeks after

the poisoning. The vascular system shows marked involvement, and localized hyperemias, cardiac palpitation, and irregularity often occur for indefinite periods afterward. Persistent gastro-intestinal disturbance is not uncommon. Icterus has been seen in rare instances and a striking sequel is glycosuria. A great variety of skin lesions have been met with.

The most important sequelæ involve the nervous system. Neuritis, usually localized, with paralysis and anesthesia, neuralgias, choreiform movements, intention tremor, scanning or stuttering speech, and incontinence of urine have been seen alone or associated with other symptoms. Cases with symptoms of Landry's paralysis or of distinct multiple sclerosis have been described. Ocular disorders are not very common; there may be partial or complete blindness of varying duration, with or without ophthalmoscopic changes, xanthopsia, nystagmus, and paralyses of the eye muscles, and there have been repeated instances of complete ophthalmoplegia with marked protrusion of the eyeballs. Occasionally, deafness or roaring noises in the ears develop; persistent headache sometimes follows. The most common and the gravest nervous sequelæ are those due to cerebral changes; these may be local or diffuse and the results are chiefly paralyses or mental disturbances; the paralyses from this cause are, of course, likely to persist; they may be monoplegic or hemiplegic. The mental disturbances vary much in type; they include simple hallucinations, simple confusion of more or less pronounced degree, very remarkable instances of amnesia or mania; but most commonly, the mental disturbances are confusional states or, in persistent cases, actual dementia.

The better recognized symptoms of *chronic* poisoning are headache, vertigo, nausea, and sometimes vomiting; there is general weakness, languor, and, in addition, usually some mental disturbance, lack of concentration, sluggish, intellectual action, or poor memory. These symptoms tend to increase, and may be associated with weak or absent tendon and pupillary reflexes. The typical picture of parietic dementia may develop. Polycythemia and leukocytosis are conditions very frequently described.

Diagnosis.—This depends upon the history or demonstration of the presence of carbon monoxide in the blood. Tests for the latter are Hoppe-Seyler's sodium hydrate test and his spectroscopic test. The sodium hydrate test is made with a solution of about 1.030 specific gravity; add this to the blood, and with carbon monoxide poisoning the result is a clotted mass of bright-red color, while normal blood gives a mucoid-like mass of greenish-brown color. The spectroscopic test depends upon the fact that carbon monoxide hemoglobin is not reduced by such substances as ammonium sulphide. Oxyhemoglobin and carbon monoxide hemoglobin produce two absorption bands that are much alike, the chief difference being that the carbon monoxide hemoglobin bands are somewhat nearer the violet end of the spectrum. If, however, ammonium sulphide is added, normal blood shows the single band of reduced hemoglobin, though this often becomes accompanied soon after by the hematin band; ammonium sulphide, on the contrary, does not affect the carbon monoxide hemoglobin spectrum, and the absorption

bands therefore remain as before. With some care they can be easily distinguished from the two bands due to reduced hemoglobin and hematin, for the hematin band lies in the red, while the carbon monoxide bands are both in the yellow. Other good tests are those of Katagame and of Kunkel-Welzer. Tests may be made with copper salts and lead acetate; the precipitate that they produce with carbon monoxide blood is bright red, while with normal blood it is a dirty dark brown color.

The poisoning should be easily recognized if the history is clear, but may readily be misinterpreted if the source is not known. Acute attacks are likely to be mistaken for alcoholism or uremia. Among the points distinguishing them from the former are the absence of odor of alcohol, the marked hyperemia of the surface, and the chemical blood tests. Uremia is distinguished chiefly by the urinary conditions and the cardiovascular changes, together with the history and the absence of carbon monoxide in the blood if tested for. Proper consideration of the occupation will often lead to a correct diagnosis of chronic cases.

Prognosis.—In acute cases this depends largely upon the exposure, but much more upon the rapidity with which treatment is undertaken. Patients usually recover if they are promptly and energetically treated; in five years 39 cases were received in the Episcopal Hospital, Philadelphia; of these, 34 recovered, and of the fatal cases several were due to late complications. Even with recovery from acute symptoms, the prognosis should be guarded for at least a month or six weeks, until it is determined that sequelæ are not about to follow, for some of the most serious after-effects have ensued upon mild poisoning. Sequelæ due to central nervous lesions are especially unfavorable. The chronic poisonings are of good prognosis if they have not caused distinct mental changes.

Treatment.—The treatment of acute poisoning consists in immediate removal from the poisoned atmosphere, free use of oxygen inhalations with the pulmotor, venesection followed by direct transfusion of blood or by intravenous or hypodermic administration of normal salt solution, artificial respiration if necessary, and the generous exhibition of stimulants (caffeine, digitalis, strychnia) if they are required. Persistent treatment will bring most patients out of even the most desperate straits. For the various late-occurring symptoms, no special line of treatment can be laid down.

II. CHRONIC CARBON BISULPHIDE POISONING

Carbon bisulphide is to a certain extent used in this country in making the cheaper grades of rubber clothes and also some other rubber articles, especially those that are not intended for long service. This form of poisoning is rare, though it is probable that there is but a limited appreciation of the fact that carbon bisulphide is freely used in certain industries and that it produces poisoning in those employed. The clinical picture of the poisoning is extremely varied, and there are no symptoms that directly indicate the nature of the intoxication.

Etiology.—Poisoning with this substance occurs almost entirely as an occupational condition. Carbon bisulphide is used chiefly to soften india-rubber so that sulphur may the more easily penetrate and exert its vulcanizing effect. The bisulphide is very volatile, and since, in the vulcanizing process, the vats containing it are of necessity open, exposure can with difficulty be avoided. The health of the workmen was so frequently and so seriously affected, that in France, governmental action was taken to control the use of carbon bisulphide. Since then comparatively few cases have been reported in French workmen. In more recent times many cases have occurred in England and Germany, Laudeheimer having reported over 50 cases in Leipsic within thirteen years, and from one factory in which only 10 persons did vulcanizing, 6 cases of psychosis were sent to the Leipsic Psychiatric Clinic in the period 1885–87. Rebuilding and instituting hygienic arrangements in this factory were so effectual that no cases were received from it in the ensuing four years. In this country carbon bisulphide is probably not used extensively in more than half a dozen rubber factories, and but very few cases of poisoning occur.

Other occupations have caused intoxication. Chemists, for example, use carbon bisulphide and in certain lines of work employ it freely and frequently, and this has caused grave chronic poisoning.

Pathology.—Beyond some emaciation, definite and constant effects do not seem to occur except in the nervous system. Pigmentation of various organs has been noted. Changes in the red-blood corpuscles and methemoglobinuria have been observed. In human cases no noteworthy blood changes are found. The cause of death in acute poisoning seems to be respiratory paralysis and asphyxia (Lewin, Koster), and any blood changes seen in chronic cases are probably due largely to mild chronic carbon-dioxide poisoning. The nervous system suffers severely, however, and there are degenerative changes in the medullary sheaths throughout the nervous system, less marked in the nerve roots and peripheral nerves than in the central nervous system; in the ganglion cells fatty degeneration is common.

Mode of Entrance and Pathogenesis.—Inhalation is the usual mode of entrance. The poison seems to have a special affinity for the central nervous tissue. Acute human or experimental poisoning resembles that due to alcohol or to the anesthetics in that it produces excitement followed by narcosis, and in chronic cases the effects may resemble chronic alcoholism; but the actual chemical action has not been determined.

Symptoms.—Some emaciation is common; nausea or vomiting and constipation may occur early; eczema is sometimes observed; strangury has been noted. The earlier stages of poisoning are often associated with sexual excitement, while in the late stages, sexual power is usually reduced or lost. Women show menstrual anomalies, and, if pregnant, abort or miscarry.

Headache, visual disturbances, vertigo, palpitation, frightful dreams, insomnia, mental depression, and apprehension without distinct psychosis, may be present in the earlier stages. Anesthesia is extremely

common. It may be limited to the area of distribution of one or more nerves and may be associated with other signs of mononeuritis or polyneuritis. Not infrequently there is hemianesthesia, diffuse anesthesia, or local areas of distinctly hysterical type. Delayed sensation may be seen. Paresthesias of various kinds and of varied distribution also occur. Hyperesthesia occurs, particularly in the feet, or more commonly in the ovarian region, in cases with hysterical symptoms. Spontaneous pain, especially along the course of the nerves, is sometimes quite marked (Delpech, Rosenblatt, Hertel).

The special senses are frequently affected, particularly vision and taste. Ring vision, macropsia, micropsia, obscuration of vision, chromatopsia, *muscæ volitantes*, and other disturbances may be present with or without signs of organic lesion. Amblyopia is extremely common even early in the poisoning. A persistent taste of carbon bisulphide is a common complaint, or everything may taste sweet or bitter. Disturbances of smell, especially a constant odor of carbon bisulphide, have been repeatedly observed, and unilateral or bilateral deafness or roaring noises in the ears.

The reflexes, both superficial and deep, may be normal, excited, reduced, or lost. There may be also disturbance of the sphincter of the bladder. Motor symptoms are very common. Tremor is occasionally observed; in some cases it is at times associated with symptoms that produce a resemblance to general paresis or to chronic alcoholism. Ataxia is often present. The most important motor symptom is paresis or paralysis, paresis being the much more common. In severe form it is most frequent in the peroneal muscles. The paresis also frequently involves the hands and arms, and a feeling of general weakness is a common, indeed, an almost constant, complaint, even in the early stages of poisoning. This weakness may be of the most extreme severity so that the patient may become unable even to feed himself. Paresis may be of one extremity alone, or of both legs or arms or of half the body; and the actual paralysis that occasionally appears may have a similar distribution, producing monoplegia, hemiplegia, or, more commonly, paraplegia. Muscular irritability is often increased in early stages and there may be cramps and local spasms. General convulsions are a peculiar feature of the acute poisoning and they may occur in severe chronic poisonings. Contractures may follow paralyzes.

Psychic disturbances are common. Transitory attacks of hilarity and general exaltation resemble acute alcoholism. There may be delirium, acute mania, and "toxic hysteria," followed by great weakness of mind and body. If the exposure continues, these attacks occur repeatedly and more readily, and a more or less prolonged psychosis may develop.

Diagnosis.—The distinction from psychic, spinal, ocular, and hysterical disorders of other source may depend upon demonstration of exposure to carbon bisulphide. *Tabes dorsalis*, central nervous lesions and alcoholism are extremely closely simulated. Hysteria is very likely to be diagnosed in a considerable proportion of cases, but more careful study will frequently show evidences of organic lesion.

Prognosis.—Mild transitory attacks of psychic or other disturbances are not likely to be followed by any permanent results unless exposure continues; when the exposure does continue and repeated transitory attacks of intoxication occur there is serious danger of a grave psychosis. The outlook in these cases has already been indicated. The cases with spinal symptoms and those with peripheral symptoms usually recover slowly, but if they have lasted for a long time and the symptoms are very severe there may be little or no improvement. The general depression of health and the hysterical symptoms, muscular weakness, etc., appear to last for a long time. The eye symptoms are often persistent.

Prophylaxis and Treatment.—Prophylaxis should be of very specific character. Workmen should wear gloves and use instruments for dipping the material into the carbon-bisulphide mixture instead of exposing their hands, and they should also be taught to exercise extreme care about exposing themselves to inhalation of the vapor. Proper ventilation must be secured by means of special apparatus. When the poisoning has developed, treatment is largely a question of absolute removal from exposure, symptomatic drug treatment when necessary, fresh air, good food, and proper elimination. Oxygen inhalations have been recommended. Alcoholic, sexual, and other excesses should be rigidly excluded.

POISONING BY THE FUMES OF NITRIC OXIDE

The increasing use of nitric acid in the arts and trades is giving rise to cases of poisoning by nitric-oxide fumes, N_2O_4 . Contact of the strong nitric acid with any organic body is all that is necessary to produce the nitrogen tetroxide, the poisonous element, which may be inhaled in a 1 per cent. mixture with the air, without the usual irritative warnings, and produce a rather characteristic condition. Some hours after exposure and even after a period of comparative comfort, intense dyspnoea with signs of acute oedema of the lungs appears, and death from suffocation may take place rapidly. Thus 55 of Schuberg's 213 cases ended fatally, after an illness varying from a few hours to several days;¹ pulmonary oedema and congestion with bronchopneumonia are the common lesions in the cases of short duration; emphysema, proliferation, and desquamation of the epithelium of the bronchioles and interstitial changes may supervene in the more prolonged illnesses. Prophylactic supervision of the storage conditions of nitric acid is vital. The breaking of a carboy on a wooden floor in a confined space may be a real catastrophe. Treatment is practically unavailing.

¹ Wood, *Arch. Int. Med.*, 1912, x.

CHAPTER XI

ALCOHOL, OPIUM, MORPHINISM, COCAINE

By ALEXANDER LAMBERT, M.D.

ALCOHOL

Etiology.—An unstable nervous system is the fundamental basis on which habitual alcoholic excesses develop. There is the weakness of will, the tendency to overindulgence, the lack of self-control, and when once the narcotic effect of alcohol is felt, the inevitable craving for more cannot be resisted. In these weak individuals there is often the marked self-conceit which deludes them into the belief that they can resist when they wish and that further indulgence will make no difference. Among the very poor the grinding weariness of overwork and insufficient food drive them to seek relief in alcohol, and before long what was a luxury becomes a necessity. The false idea that alcohol is a tonic and strength-producer causes many of the poor to give alcohol to their children and thus lay the foundation for early excess. In Bellevue Hospital, New York, in 259 young male alcoholics in whom there was no mental degeneration from chronic alcoholism and whose statements may be deemed fairly accurate, 4 began before six years of age, 13 between six and twelve, 60 between twelve and sixteen, 102 between sixteen and twenty-one, 71 between twenty-one and thirty, and 8 after thirty years of age. Almost all gave a history of intemperance in other members of their families. The force of example is often a potent cause of alcoholism; the fear of ridicule from their comrades and what is thought to be social necessity or a vain desire to be thought manly, are also factors in certain individuals. Lives of idleness and pleasure-seeking among the wealthy not infrequently lead to alcoholism. In this country there is a not uncommon cause in the use of patent medicines and nostrums. A large number of these contain from 6 to 47½ per cent. of alcohol and they seem to be popular in ratio to their alcoholic content. Many acquire alcoholic habits in their endeavors to alleviate the pains of disease.

While the environment of certain occupations is a factor in producing alcoholism, in other situations it produces temperance. The demands of modern machinery and electrical devices require a clear mind and steady hands, both for the production of good work and for self-protection, so that employers are more and more demanding sobriety among their employees. In the large centres of population these have been potent factors in the diminution of alcoholism among the younger working men. Judging from some 10,636 male alcoholics admitted to Bellevue Hospital, New York, the professions in which mental strain with worry, excitement, and especially irregular hours are a predominating

factor, show a larger proportion of alcoholics than those in which such conditions are less pronounced. Journalists, actors, and physicians are more prone to alcoholism than lawyers, engineers, and other professional men. Book-keepers, clerks, accountants, and stenographers seem to show a high proportion who drink to excess. A craving for excitement as a reaction to a monotonous existence, may account for the large numbers in this class of occupation. Those demanding physical exertion near fires, such as stokers, firemen, blacksmiths, iron and brass moulders, have long been recognized as producing a craving for alcohol. Stable men, hostlers, hackmen, and teamsters of all kinds, men whose occupations vary with periods of hard work and rest and idleness, together with exposure to varying weather, form a large class who unfortunately acquire their habits of intemperance in the early and most productive years of life. The age of more than half of the admissions in the large numbers belonging to these occupations was from five to fifteen years less than the age at which the greatest number of alcoholics was admitted to the hospital. Among the large number of men employed in the building trades in New York, alcoholism predominated in the following order: stone-cutters, plasterers, painters, masons, roofers and coppersmiths, plumbers and carpenters. From the opportunities and temptations of their occupation, saloon-keepers, bartenders, and waiters show a high ratio of alcoholism. Among some 2700 female alcoholics admitted to Bellevue Hospital, housework and domestic service was given as the occupation in more than half, but this, in a large but unknown number, really hid prostitution. Laundresses and cooks predominated among those whose definite domestic service was given. Seamstresses, dressmakers, and milliners comprised about 6 per cent. of the admissions and were more numerous than women working in factories and shops. The difference between the sexes among those who drink to excess may best be summed up by saying that men will drink to excess for any cause which for the moment may seem sufficient. Women rarely drink to excess except for the purpose of hiding or forgetting something which they are unwilling or unable to face.

The influence of heredity is believed by some to be more potent than environment. Plutarch's saying that "drunkards beget drunkards" has been long recognized. Many descendants of alcoholic parents inherit a weakened and unstable nervous system. The craving for alcohol in the parent is not inherited but a weak and unstable nervous system which renders the individual liable to excess, and slighter indulgences lead quicker to the formation of the alcoholic habit.

It is of interest to note the relation of *age* to the admissions for various forms of alcoholism in Bellevue Hospital. For comparison, the ages of 10,636 male and 8132 female admissions were taken. The largest number of admissions for males occurred in the period 33 to 37, and the largest number of females in the period 28 to 32. The greater relative number of young women is due to the facts that alcohol usually poisons women quicker than men, and among the working classes, the men, by a larger amount of muscular work, burn up more alcohol and thus escape some of its toxic action. These statistics are also influenced by

the number of young prostitutes who are necessarily included in the statistics from any large city. Alcoholism is more prevalent among men than women; during the ten years, 1895 to 1905, there were two and a half times more men than women admitted to Bellevue Hospital suffering from alcoholism.

The effect of season and other external influences is well shown by the admissions for alcoholism for the ten years, 1895 to 1905, in Bellevue Hospital. The total admissions in the alcoholic wards in that time were 43,916 males and 16,076 females. Considering the male and female curves for each of the ten years, there are some variations which are not shown in the average curve for the ten years. Periods of great heat cause a marked rise in the male curves but only a slight corresponding rise in the female curves.

Sociological conditions, such as labor strikes, cause a great increase of alcoholism among both men and women. The variations in the Bellevue records show more varied and wider excursions in the male than in the female curves, and the rises and falls of the two curves in the same years do not always run parallel. Taking the average curves for the ten years by monthly admissions, the point of the January curves in both sexes is lower than the previous December; in February there is a distinct fall, reaching the lowest period of the year. There is a spring rise in March and April, a May fall, a June rise, a fall in July and August, a marked September rise, and here the two curves separate, there being an October fall in the male and an October rise in the female curve, the point of the October rise being the highest point for the year in the female curve, a November rise in the male, the highest point for the year, and a November fall in the female and a December fall in the male and December rise in the female curve. Both agree in having the greatest number and highest daily average during the last four months of the year. Comparing the curve of the alcoholic with those of the general medical and surgical admissions, a striking difference is evident. The two curves are practically reversed for both men and women, the greatest number of admissions for general diseases occurs in the first four months of the year. The curves for alcoholism here described are for all forms, the acute cases forming a minority.

Pathology.—Considering the effect of alcohol on the body, ethyl alcohol is the one chiefly to be considered. But in the distillation of whisky other bodies as aldehydes occur, and some of the higher alcohols usually grouped under the name of fusel oil, which deserve consideration. In the compounding of cheap whiskies and in other adulteration methyl alcohol must be considered.

Methyl Alcohol.—This is also called wood alcohol and is sold in the United States as columbian, colonial, union, or eagle spirits. In Canada, it is sold as greenwood or standard wood spirits. It is used to adulterate various essences or colognes and often to adulterate cheap whiskies. In experiments on the toxicity of the different alcohols, considering that of ethyl alcohol as 1, methyl alcohol is from 0.46 to 0.8, but this gives a false idea of its true toxicity when taken by man, although idiosyncrasies of resistance to methyl alcohol vary greatly, as the ingestion of two

teaspoonful of it has been followed by blindness; in other individuals many ounces have been taken, followed only by intoxication. Another peculiarity of methyl alcohol is that, except in very large doses, the serious toxic symptoms may be delayed for twenty-four hours or even several days. The intolerance for methyl alcohol for long periods is due to the fact that a considerable portion of it is turned into formic acid in its passage through the body. The single constant pathological changes in animals after poisoning by methyl alcohol is fatty degeneration of the liver.

Wood and Buller published 275 cases of methyl alcohol poisoning, among which there were 122 deaths and 153 instances of blindness. In New York City, in the winter of 1904-1905, there were 25 deaths from methyl alcohol poisoning, after drinking whisky adulterated with it. These authors emphasize the idiosyncrasies to the toxic effects and give three degrees of intoxication: The first shows the ordinary marked symptoms of intoxication with dizziness, nausea, and marked gastrointestinal disturbances, terminating in perfect recovery in a few days, sometimes followed by more or less serious damage to vision. In the second degree, the dizziness, nausea, vomiting and gastrointestinal disturbances are much more pronounced; there is marked cardiac depression, weak pulse, sweating and slow respiration; there may be delirium or unconsciousness which often deepens into coma and death. If coma once supervenes, recovery seldom takes place, for even if the patients recover consciousness, they usually relapse into coma and die. There is very often a sudden development of widely dilated, reactionless pupils, with complete or nearly complete blindness. After recovery, dimness of vision, often increasing to total blindness, is characteristic of this degree of poisoning. The third degree is that in which an overwhelming prostration comes on, which terminates in coma and death. Nearly all the severe cases which are not fatal, show characteristic bilateral, total blindness, coming on in a few hours or perhaps not for several days; this is followed by partial restoration of vision, which again, after days or weeks, gives place to a more or less complete and permanent blindness and atrophy of the optic nerve. In the majority of fatal cases, death seems to occur in less than twenty-four hours, though methyl alcohol may kill within an hour or death may be delayed for one or two days or even longer. The ophthalmoscopic examination shows the visual field contracted, absolute central scotomata, the nerve head first congested, followed by gray or white atrophy and contracted vessels. Pathological examination shows a retrobulbar neuritis, papillitis, other inflammatory symptoms and atrophy of the optic nerve.

In those dead from methyl alcohol poisoning, at autopsy, intense congestion of the stomach and intestines, with a characteristic odor of methylated spirits, is noticeable. For the sake of conciseness, we will consider here the treatment of methyl alcohol poisoning. The treatment of the optic nerve atrophy is not very satisfactory in severe cases, although pilocarpine, sweat baths, and potassium iodide as soon as the patient's condition permits, in the early stages of neuritis, followed by strychnine, hypodermically, seem to limit the extension of the secondary atrophy.

The general treatment consists in washing out the stomach, and vigorous stimulation by strychnine, caffeine and digitalis, hypodermically. It seems useless to give these drugs by the mouth. Ergot, hypodermically, will also be found useful. High enemata, of warm saline solution or of glycerin and castor oil, should be given.

Higher Alcohols.—These, such as propyl, butyl, and amyl alcohol, are undoubtedly more toxic than ethyl alcohol and their toxicity increases as they mount in the chemical scale. This group, with substances such as furfural, compose what is generally called fusel oil. It has often been claimed that these alcohols cause many of the symptoms of chronic alcoholism, but they practically play no rôle in the acute or chronic poisoning. It is claimed that the so-called moonshine whisky, produced in the mountains of some of the Southern States, is very deleterious if drunk when freshly distilled. The fresh rye or corn whisky would contain the greatest amount of fusel oil, for these higher alcohols are oxidized and changed into other substances, which give to old whiskies the various flavors, and the older they are, the less they contain of these substances. Huss has shown that amyl alcohol, in human beings, taken in doses of $\frac{1}{8}$ to $\frac{1}{2}$ grain, caused no toxic symptoms; doses of 1 to 2 grains were followed by sensations of oppression in the chest, with temporary feelings of dizziness; doses of from 3 to 4 grains acted as a gastrointestinal irritant, causing a burning sensation in the epigastrium, colic, vomiting and diarrhœa. He estimates that the total amount of amyl alcohol contained in twelve to fifteen glasses of brandy is only 1 to $1\frac{1}{2}$ grains, and the effect produced by this in ordinary drunkenness would practically be *nil*. Baer studied the effect of adding a definite percentage of these higher alcohols to ethyl alcohol, and found that the addition of 2 per cent. of amyl alcohol caused an appreciable increase in toxicity, and the addition of 4 per cent., a very considerable increase, so that a severe type of poisoning resulted in animals. It is evident therefore, that larger percentages of these higher alcohols than are found in even the worst alcoholic beverages must be added to ethyl alcohol, before we can attribute to them any great share in the fatal outcome of an acute poisoning. Furfural, or pyromucic aldehyde, is also present in fusel oil. Joffroy has found that the toxic equivalent of this substance is 9.14 for rabbits as against 8.20, the true toxic equivalent of ethyl alcohol for these animals. But as a liter of rum contains only 0.015 to 0.04 gram, a liter of cognac 0.005 to 0.015 grams if we assume that man is as sensitive as rabbits to furfural, it would require from 300 to 700 liters of rum or brandy to furnish the fatal dose. We must therefore leave out the consideration of this aldehyde in the conditions produced by ordinary alcoholic beverages.

Ethyl Alcohol.—This is the main constituent of most alcoholic beverages and to it are due the symptoms of alcoholism as seen in man. Spirituous liquors may be considered as acting in ratio to their alcoholic content; the wines, however, vary in their action, either from the ethers which they contain or, in some instances, so far as digestion is concerned, in proportion to the contained solid matters, rather than to their alcoholic content. The same is true of the action of malt liquors which inhibit

digestion through the extractives which they contain and further influence metabolism through their carbohydrates.

It is unnecessary to go into the minute effects of ethyl alcohol on the body or to discuss its action on the various physiological processes. Different individuals show the widest degrees of tolerance and intolerance to the same dosage. Both in its effects on the brain and in the various other viscera the same amount of alcohol seems to produce different lesions, varying in their situation and intensity. With our present knowledge of chemistry it is impossible to explain these variations. What is moderation for one individual is excess for another. It is therefore difficult to define what constitutes the moderate use of alcohol. Duclaux's definition seems the most satisfactory, namely, that alcohol has been taken to excess if an hour after its ingestion one is in any way conscious of having taken it. This is a stricter definition than would usually be considered as necessary to define moderation, but it is a limit within which the drug action of alcohol would not occur and the amount taken would in all probability be burnt up in the body without doing injury. In such moderation alcohol probably does not do more than stimulate digestion and relieve the sense of weariness. Its effect on the circulation would not go farther than a slight change in the character of the pulse, making it feel fuller and stronger. This is probably due to a slight increase in the power of the heart's action without increasing the pulse frequency and in a slight rise of blood pressure and contraction of the vessels of the splanchnic area which really produces a change in the distribution of the blood without increasing the frequency of the pulse. If the daily ingestion of alcohol stopped here, probably none of the usual morbid changes would occur. But alcohol is a narcotic and as such generates a desire for more to relieve the relaxation following its use. Some individuals are so sensitive that after a single drink of an alcoholic beverage they are not sober and with their weakened resistance they must then go on to the full indulgence of a prolonged spree. The morbid processes produced by alcohol come under three heads or a varying combination between these three: a degeneration of the intrinsic parenchyma of each viscus, a chronic congestion and degeneration of the bloodvessels, and increased connective-tissue growth or fibroid replacement of the parenchyma. This produces at first a functional disturbance, later a perversion of function, and finally a cessation and obliteration of function.

As concerns the relationship of man to his environment the effect of alcohol on the brain is a predominant manifestation, but for the individual the effect of alcohol on the heart and circulation in acute poisoning and on the heart and abdominal viscera in chronic poisoning is often more important. All the viscera are affected by chronic alcoholism, the cerebral symptoms seeming to predominate only because of the special function of the brain. Death from acute poisoning by alcohol is rare and usually follows large doses in those unaccustomed to its use, or sometimes occurs in children who have accidentally swallowed a large amount of some concentrated alcoholic beverage. The lesions do not correspond to the intensity of the symptoms. The functions of the

various organs are overwhelmed so quickly that no anatomical change appears. Death may occur within half an hour or after several hours of drinking, or fatal coma may suddenly come on after several hours. The postmortem appearances, after death from such acute poisoning, show the stomach, the œsophagus, and duodenum often of a deep red color with, at times, punctiform ecchymosis in the gastric mucous membrane. The stomach, or the tissues even, may give out a more or less well-marked alcoholic odor. There may be an acute venous congestion in some of the viscera and the bladder is often greatly distended. There is frequently congestion and sometimes extravasation of blood, or œdema in the brain and its membranes. There may be a serous effusion in the ventricles. In one woman, thirty years of age, previously a total abstainer, who took enormous amounts of alcohol, dying after four days, the brain showed acute encephalitis with marked cellular degeneration. The spinal cord showed degeneration in the posterior tracts and in the cells of the anterior horns. The peripheral nerves were normal.

Microscopically the *nerve cells* show two different lesions. One shows various swellings from varicosities in the course of the protoplasmic processes of some of the nerve cells, associated with partial loss of the delicate spinous projections normally present. The second change is that of chromatolysis and is shown by the disintegration of the small chromatin granules known as the Nissl bodies, as brought out by the stain of that name. These changes are not in ratio to the severity of the symptoms, as Welch says they do not represent any serious permanent damage to the nerve cells but are rapidly recovered from after the disappearance of the causative factor. These are not general and occur only in the minority of the cells, but have been found in the cells of the cerebral hemispheres, the cerebellum, the medulla, the spinal cord, and the sympathetic ganglia.

Personal idiosyncrasy is as marked in the lesions produced by alcohol as it is in the susceptibility to the same dose. This is true of the intensity of the lesions in any given viscus and in the distribution among the various viscera. In studying the age at which death occurs from chronic alcoholism, there is a noticeable difference between the sexes. Taking 541 deaths from alcoholism in Bellevue Hospital, New York, 318 men and 223 women, it is noticeable that the highest percentage of the men died in the same quinquennial period in which there were the greatest admissions, while the greatest percentage of female deaths was ten years later than the period of greatest admissions. Thus 20 per cent. occur in men between thirty-three and thirty-seven years of age and 19 per cent. of the deaths in women occur between thirty-eight and forty-two years of age. This is undoubtedly due to the prevalence of pneumonia at this age. Between thirty-three and forty-two years of age both sexes show practically the same percentage, but there is a very great difference in the number of deaths before thirty-two years of age, the percentage in men being 17.2 and in women 31.4; that is, nearly twice as many young women die of alcoholism as young men. The fact that a large number of young prostitutes are necessarily included accounts for the large number of women dying from alcoholism. To

obtain an idea of the lesions in chronic alcoholism, the records of 125 cases were taken from the postmortem reports of Bellevue Hospital, 90 of which were of men and 35 of women. Many histories with pneumonia have been rejected.

In the *heart*, fatty degeneration of the muscle is the most common lesion, brown atrophy combined with fatty degeneration is the second, brown atrophy alone the third, and fibroid myocarditis the fourth. There were often combinations of the above lesions, and while fatty infiltration is said by most observers to be more common than fatty degeneration, the reverse held true in this series. That brown atrophy of the cardiac muscle is caused by alcohol seems to be undoubted, because it was present in one-fifth of the hearts examined in the individuals under fifty-five years of age, considering only those records in which carcinoma and healed or active tuberculosis could be excluded. The secondary effect of alcohol on the heart is shown through the circulatory system and from disease of the coronary arteries we obtain fibroid myocarditis; the enormous hypertrophied heart of beer-drinkers is due to the large amount of fluid. The arteriosclerosis, produced by alcohol or secondary to the kidney lesions produced by it, is also a cause of cardiac hypertrophy and later of the fibroid myocarditis. Sudden death often occurs in young alcoholics who, possessing a heart with fatty degeneration, further poison it with alcohol, and when some sudden muscular action causes a sudden strain, the cardiac muscles fail, and death results. The arteriosclerotic degenerations show most intensely in the aorta, in the great vessels, and in the ramifications of the abdominal vessels. Cabot claims that general peripheral arteriosclerosis is only seen in 6 per cent. of alcoholics. This is undoubtedly true, and yet very extensive changes are often present in the aorta and abdominal vessels of patients who show no peripheral arterial changes.

In the *lungs* the lesions found were oedema, congestion, and various forms of pneumonia. It is very common to find tuberculosis in various stages. Pulmonary emboli from cardiac thrombosis and embolism of the pulmonary artery were also found in this series.

In the *liver* the combination of cirrhosis, brown atrophy, and parenchymatous degeneration, with fatty degeneration, was found in 80 per cent. of the men and 74 per cent. of the women. Fatty degeneration combined with cirrhosis was the second most common lesion. Fatty degeneration of the liver is found among those who take large amounts of malt liquors; cirrhosis is usually found in those who drink heavily of wines, whisky, gin, or rum. In this series of autopsies it was present in 48 per cent. of the men and 34 per cent. of the women, and it seems to occur in those persons who, possessing a high degree of tolerance for alcohol, are enabled to consume enormous amounts. It is a noticeable fact clinically that men whose nervous tissues possess a high degree of tolerance are those who find themselves in middle life with cirrhosis of the liver and degenerated viscera. Those who possess an intolerance for alcohol in their nervous tissues are the ones who mentally go to pieces early, and though more often noticeably drunk, less frequently show degeneration of the abdominal viscera.

In the *spleen* chronic congestion and fibrosis were the two most common conditions. Acute congestion occurred next in frequency; other conditions found were brown atrophy, amyloid degeneration, hemochromatosis, and brown atrophy. A very noticeable feature is the frequency with which chronic fibrosis occurs in the *pancreas*. A moderate percentage of fatty infiltration occurred in both men and women and the *pancreas* was normal in one-fourth of the patients examined. The *adrenal bodies* were normal in a little over one-half of the men and one-third of the women, but in one-third of the men and in over one-half of the women examined there was a fatty degeneration of the cortex.

In this series a very noticeable feature is the fact that there were no records of normal *kidneys*; all examinations showed some lesions, chronic ones greatly predominating. Acute nephritis was mentioned in only two men and one woman. Acute exacerbation in chronic nephritis was present in seven men and one woman. Chronic parenchymatous nephritis, often with congestion, was the most common lesion, being present in a little less than two-thirds of both sexes. Chronic interstitial nephritis, at times with congestion, occurred in about one-third of the cases. As these examinations were made on patients of from twenty to over seventy years of age who had died from chronic alcoholism, it would seem to show that while the kidneys for years may escape, sooner or later they are certain to become diseased.

The *stomach* shows various forms of gastritis, chronic gastritis being one of the commonest lesions. An inflamed gastric mucosa, covered with ropy mucus, is common from acute alcoholism and sooner or later goes on into the chronic form. Chronic atrophic gastritis was present in half of the cases. Hemorrhagic gastritis was present in about one-fourth of the men and one-eighth of the women. These were not infrequently combined. The mucosa of the intestines does not suffer so much as the gastric mucosa. The most common condition found was congestion, sometimes with œdema. In about 50 per cent. of the patients examined the intestinal mucosa was normal.

The bladder is often overdistended in patients who have died suddenly or had unconsciousness before death. It may be ruptured, as was the case in two men in the service of the author. In about one-fourth of both sexes either acute or chronic cystitis was found.

That alcohol tends to produce *sterility* has long been known. In 5 among 12 women between twenty and thirty years of age, the ovaries were markedly atrophic, appearing like those a number of years after the menopause, and in women between thirty-one and forty, they were atrophic in 5 among 8. Thus in 10 of 20 women under forty years of age they showed extensive atrophy. Bertholet has also reported an atrophy of the ovary and ova in female alcoholics. In the men the testicles did not show gross evidences of atrophy, but in the few examined microscopically there was sclerosis. Bertholet found partial or extreme conditions of atrophy of the testicles in the majority of 75 chronic alcoholics. Lancereaux has also proved this, and Simonds observed that in 60 per cent. of chronic alcoholics on postmortem examination

azoöspemia was found. Broun and Garnier have confirmed these findings by animal experimentation.

Some individuals will die of various somatic degenerations and still retain apparently normal cerebral tissues, while in others the brain and spinal cord seem to suffer early, and disproportionately, compared with the heart and abdominal viscera. The lesions in the central *nervous system* seem to be brought about either from the degeneration of the cerebral arteries or by the direct action of alcohol on the nerve cells. It is often impossible in any given brain to differentiate the changes due to one or the other of these causes. The membranes usually appear congested with an increase of fluid in the pia arachnoid space. This fluid has been shown by Stillman to be particularly common in alcoholics and to be due to a replacement equalizing the diminution in the size of the brain. This diminution may be due either to the gradual normal diminution in size with age or to an actual shrinkage due to an increase of connective tissue and an atrophy of the cerebral tissues. It occurs more commonly in the chronic alcoholic than in patients dying from other diseases, although it is also found in other conditions. Added to this fluid and meningeal congestion, it is recorded that there was œdema of the cerebral tissues in about three-fourths of the brains of men and about one-half of those of the women examined. Congestion of the cerebral tissue was found in 54 per cent. of the men and 14 per cent. of the women. Pachymeningitis was not uncommon and pachymeningitis hemorrhagica is frequently seen in alcoholics, probably from trauma acting on the diseased vessels. All inflammations in alcoholics seem to be prone to the hemorrhagic type and hemorrhagic meningitis was present in three men. The degeneration of the vessels produced miliary aneurisms and it is not uncommon to find recent cerebral hemorrhages, encysted old hemorrhages or areas of cerebral softening from embolism.

Microscopic examination shows an intense degree of atheromatous degeneration of the minute vessels which are enlarged, often tortuous, unevenly distended, usually by fusiform dilatations, and their tissues covered with nuclear proliferations. Not infrequently the vessels are plugged and the diseased wall ruptured with extravasated blood and hematoidin crystals in the surrounding areas.

In *delirium tremens* there is a distinct tendency to minute acute hemorrhages which are diffusely scattered in the cerebral cortex in the central and frontal convolutions, less frequent in the cerebellum and still less in the spinal cord. The place of predilection is the region of gray matter around the third ventricle in the aqueduct of Sylvius. These hemorrhages are very commonly observed in the region of the nuclei of the oculomotorius and abducens nerves. About the bloodvessels the spider or glia cells are crowded in great abundance. These are densest just underneath the pia and form a thick connective-tissue felting which converts the outer fourth of the cortex into a closely matted layer, much diminished from the normal thickness and often clearly mapped off from the layers beneath. The second and third layers of the cortex show but little change. The fifth layer of motor cells shows extensive fatty degeneration, and, with the spider cells beneath, is undergoing disin-

tegration and absorption. The changes in the spinal cord are similar to those in the cerebral cortex. The vessels of the posterior and lateral columns are more involved than those of the anterior columns. The characteristic change is an obliterating endarteritis, the lumen of the vessel being encroached upon to such a degree that the intima is folded into ridges. At times the vessels are completely occluded. The connective tissue processes from the pia into the cord are thickened, the median raphe of the posterior columns and the peripheral zone of the cord being the areas of election for the sclerotic processes. The anterior and posterior roots are sometimes involved. The degenerative processes may be unilateral or bilateral and the various segments of the cord show varying and irregular degrees of involvement.

In a series of cases of alcoholic *neuritis* in Bellevue Hospital, Harlow Brooks, with whom the work of the author in the pathology of alcoholism has been done, has studied the central nervous system and peripheral nerves. In one patient the peripheral nerves alone showed degenerative changes. The most diligent search with the Marchi method failed to show any corresponding changes in the cord. It is possible, therefore, that alcoholic *neuritis* may be due to involvement of the peripheral nerves alone, but we believe that this is very exceptional. In some of the other cases there was marked degeneration in the cortical cells of the cerebrum, especially in the motor areas, accompanied by degeneration of descending fibres in the internal capsule and in the descending columns of the spinal cord; not a true tract degeneration but one of isolated and often widely separated fibres. In the spinal cord extensive cytoplasmic degeneration was present in the ganglion cells of the anterior horn, the ventrolateral group being especially studied, and there were invariably isolated degenerated fibres in the anterior nerve roots. Degenerated fibres were found in the ascending tracts of the spinal cord, particularly in the severe cases, this being accounted for by alterations, at times very marked, in the ganglion cells of the posterior roots. In some cases ascending and descending degenerations were present in the same spinal cord. Similar results have been found by other investigators.

The pathology of *Korsakow's psychosis* is a combination of what has already been described. This has the dura adherent to the skull, the thickened pia with its gray striations along the course of its vessels, the diffuse cerebral atrophy and increase of the connective tissue, the cellular degenerations shown by Nissl's staining and other changes produced by chronic alcoholism. There is the same tendency as in delirium tremens to small hemorrhages in similar positions as described above. The spinal cord shows degenerations in the various tracts and of the spinal neurons. The peripheral nerves show the various lesions of *neuritis* or stages of reconstruction.

It is supposed that alcohol reduces the resistance to infectious diseases. This is undoubtedly true in temperate and northern climates. In the tropics, while the statistics from the British army seem to prove the same for India, Major Woodruff gives statistics for the American troops in the Philippines which show that moderate and even excessive drinkers, after two years' residence, were in far better health and more resistant

to disease than total abstainers. In the temperate zones an attack of infectious disease in a chronic alcoholic is extremely prone to cause delirium tremens and the prognosis is always grave. Barthelémy emphasizes the fact that waiters and workers around saloons acquire an especially severe form of syphilis. Bârs clearly shows that in epidemics of cholera the disease claims the majority of its victims among the alcoholics and when they are attacked, the chances of recovery are relatively small. In pneumonia the mortality among alcoholics greatly exceeds the average. In Bellevue Hospital in 1904 there were 1001 patients with lobar pneumonia; of these 667 gave a history of alcoholism. Among these the mortality was 50 per cent. and among the non-alcoholics 23.9 per cent.

The results of chronic alcoholism unfortunately do not end with the individual. The children of alcoholics often come into the world as idiots or weak minded. Recently, Stockard has proved by animal experimentation that alcohol readily affects the offspring through either parent and his experiments seem to indicate that the tissues of the nervous system of the offspring are particularly sensitive in their responses to the induced conditions. Nicloux and Renault, according to Stockard, have shown that alcohol has a decided affinity for the reproductive glands. In the testicular tissues and seminal fluid an amount of alcohol is soon present which almost equals that in the blood of the person having recently taken alcohol. The proportion of alcohol in the testis as compared with that in the blood was as 2 to 3 and in the ovary of female mammals as 3 to 5. The genital glands show as great an affinity for this substance as the nervous system. It must necessarily follow that alcohol may act on the ripe spermatozoön shortly before the time when it fertilizes the egg, and since an affected spermatozoön may give rise to a defect in the individual, we have a probable explanation for many of the recorded defects attributed to drunkenness at the time of conception. A male in a state of acute intoxication, is more apt to beget an abnormal offspring than is a non-intoxicated male, although a frequent user of alcohol. The experimental data on the sensitiveness of the spermatozoön and the observations on the presence of alcohol in the seminal fluid warrant this statement. Lippich observed 97 children resulting from such conceptions and only 14 were without noticeable defects. Sullivan reported 7 cases of drunkenness during conception which are fairly authentic. Six of the children died within a few months after birth and the seventh was stillborn.

Schweighofer has recorded an interesting individual case. A normal woman married a normal man and had 3 sound children. The husband died and she married a drunkard and gave birth to 3 other children; 1 of these became a drunkard, 1 had infantilism, while the third was a social degenerate and drunkard. The first 2 of these children contracted tuberculosis which had never before been in the family. The woman married a third time and by this normal husband she again produced sound children.

Bourneville, in Paris, found that of 1000 idiot epileptics and weak-minded children 471 had a father who was alcoholic, 84 an alcoholic mother, and in 65 both parents were drunkards. In Normandy, Dahl

found that 50 per cent. to 60 per cent. of the idiot children had either an alcoholic father or mother. It was noted that in Norway from 1825 to 1835, following the free distillation of brandy, drunkenness was enormously increased and simultaneously the number of idiots increased 150 per cent. Afterward, in the ten years from 1855 to 1865, when the consumption of brandy had greatly diminished, the number of idiots diminished 16 per cent. simultaneously with an increase in the population of 14 per cent.

Bezzola, in Switzerland, studied 70 cases of pronounced idiocy and found that half of these idiots were generated during the wine harvest while the rest were divided evenly during the remaining thirty-eight weeks in the year. He further shows that the majority of 8190 idiots were born in the wine districts, and again the season for the maximum birth of such children was nine months after the great national feasts. The normal generation curve of Switzerland showed further that during these same periods of feasting there was a noticeable diminution in the number of children generated.

Epilepsy in children often follows alcoholism in the parents. Spratling mentions that while alcoholism is not usually a direct cause of epilepsy in women, it is frequently an indirect cause through its presence in the parents, nearly always in the father. Kawalewsky, in Krakow, could prove drunkenness in 60 per cent. of the epileptics. Blueler in Switzerland, could prove drunkenness in the progenitor of 70 per cent. of his epileptics. Congenital deafness and dumbness do not seem to be produced by alcoholism in the parents in any large number of the children with these afflictions. Chronic hydrocephalus seems to be more frequently the consequence of alcoholism in the parents, for, in Berne, 23 of 38 children suffering from this disease had alcoholic parents; in Paris, 18 out of 23 had drunken parents.

That alcohol tends to the degeneration of the race and after a few generations to extinction, has been abundantly shown. Demme compared ten alcoholic families with ten non-alcoholic families. Only 17.5 per cent. in the alcoholic families were healthy, while practically only 18 per cent. of the non-alcoholic families were not healthy. Sullivan found that from 120 female alcoholics there were 600 children, and of these 335 died under two years of age or were stillborn; in more than 60 per cent. of these cases the children died from convulsions. He found that 21 of these alcoholic women had sisters or daughters who were abstinent and who had children from temperate men. These 21 alcoholics had 125 children of whom 55.2 per cent. died before the second year of life, and the 28 non-alcoholic women had 138 children, of whom 23.9 per cent. died before the second year of life. The mortality of children from alcoholic mothers is thus two and one-half times greater than from non-alcoholic mothers in these statistics. Animal experiments show the same relative mortality between alcoholic and non-alcoholic animals.

Delirium Tremens.—Etiology.—Delirium tremens develops on the foundation of chronic alcoholism. Its occurrence does not run parallel to the amount of alcohol taken, for idiosyncrasy is usually as strongly marked here as in all conditions in which alcohol comes in question.

Many men who have never been intoxicated, but who have for years steadily taken alcohol, will, after some severe accident, develop delirium tremens. Its occurrence so far as climate, age, and sex are concerned, is the same as for chronic alcoholism, but it differs essentially in its seasons of greatest frequency and is dependent for its development on other causes, which are engrafted on the chronic alcoholism. It occurs more frequently in northern regions and in the great industrial centres. Where beer and wine are the predominating drinks, delirium tremens is less frequent than in the countries in which men drink spirits chiefly. It has been claimed that since the distilled liquors contain less fusel oil there are fewer numbers of delirious cases, but it is doubtful whether any such deduction is justifiable. The writer has often noticed that delirium tremens patients who had consumed only high-grade whisky, seem to clear up quicker than those who had consumed a cheaper grade, but even in these cases the doubt always remains whether or not less ethyl alcohol has been consumed.

The time of year shows a distinct influence on the number of delirious cases. Bonhoeffer, in Breslau, says that the winter months, January, February, and March, show the lowest numbers; from April on there is an increased frequency which reaches its highest point in July and August. The curve maintains almost the same rise through September, and falls rapidly in November and December. The occurrence of delirium tremens in Bellevue Hospital corresponds with the above statements in so far that sudden heat always shows an increase, but there are more patients suffering from delirium tremens during the winter months than in the spring and fall, and the number during the cold months is equal to or even greater than during the hot months. This is due undoubtedly to the large number of pneumonia patients and to the greater number of accidents in the cold months, but even after deducting these, the total remaining is as high among some of the cold months as during any of the hot months. These statements are based on the statistics of 1066 cases of delirium tremens occurring between January, 1904, and July, 1905. It would seem that the varying occurrence of delirium during various seasons of the year is largely affected by other accidental causes which do not seem to act in different places with even intensity. The previous duration of chronic alcoholism seems to have more influence, and it is said that the average is from six to ten years, although according to Jacobsohn it is never less than seven years. The age at which delirium tremens develops is the same as that in which chronic alcoholism is most common, that is, between thirty and fifty years. In children it is rare. Bonhoeffer quotes one of sixteen years of age, and the writer saw one boy of fifteen years. It occurs most frequently in men, doubtless because they are more exposed to various accidents, which tend to bring about an outbreak. By some it is claimed that the delirium in women is shorter and less severe than in men; this does not correspond with the opinions of others, although in my experience the delirium in women is usually of a less violent type. It is impossible to say to what extent inherited or acquired mental degeneration influences the occurrence of delirium tremens but that such defect of mental vigor is present in the majority,

is beyond question. It seems certain that succeeding attacks of delirium tremens are more easily brought about than the primary one.

Accidental causative factors producing delirium tremens have long been recognized, such as acute infections, trauma, hemorrhage, epileptic attacks, the sudden withdrawal of alcohol, sudden intensity of alcoholic excesses or mental shock. Bonhoeffer, in 250 cases of delirium tremens, could prove in 70 per cent. a recent acute illness or delirium occurring as a complication of it. Undoubtedly the most common acute infection which brings about delirium tremens is pneumonia. Jacobsohn in 281 delirious patients found pneumonia in the ratio of one to eight; in 1066 patients in Bellevue Hospital, pneumonia occurred in every fifth patient. Traumatism, such as fracture of the ribs, legs, arms, and skull, very frequently caused an outbreak of delirium tremens, although the percentage in which these occurred is much less than the acute infections. In our experience it is a noticeable fact that severe dislocation at the shoulder or elbow is not so frequently followed by delirium tremens as fractures of the long bones. Bonhoeffer believes that injuries to the breathing apparatus are especially likely to be followed by an outbreak of delirium. Many others lay great stress on epilepsy as a causative factor, but it is a question whether the epileptic seizure is not an expression of the same causative factor which later produces the delirium. An epileptic attack is given as the direct cause of the outbreak of the delirium in from 2.5 to 16 per cent. Among chronic alcoholics, epileptic attacks are very common and in the majority are not followed by an outbreak of delirium. It is difficult, therefore, to accept the view that these are the cause of delirium tremens, although one cannot deny that it is reasonable to suppose that the mental shock produced by them may at times be sufficient to accelerate the outbreak of an already developing delirium. The sudden withdrawal of alcohol in uncared-for patients, in whom no attempt is made to replace it by proper treatment, is at times the cause of an outbreak. This is due to the sudden change of the conditions of life, for when individuals are properly treated, the sudden withdrawal of alcohol does not produce delirium. That delirium tremens is caused by some factor outside of chronic alcoholism seems undoubtedly true, but the definite specific cause is unknown.

Symptoms.—The outbreak of delirium tremens is never sudden; there are always premonitions. The patient becomes peevish, excitable, and restless, loses sleep, and when he falls into slumber, is disturbed by dreams from which he starts in anxious fear. Beginning hallucinations appear which he recognizes as dreams, but although he knows they are unreal, they still disturb him. He often feels oppression around his heart which may increase to precordial pain; there is singing in his ears, which may develop into voices scolding, abusing, or even threatening him; the dizziness increases; the tremor becomes more marked especially in the hands and tongue. This incubation period may extend over several days or, according to Kraft-Ebing, as long as twelve days. Where the delirium occurs in the course of pneumonia it appears generally on the third or fourth day, and, following an accident or fracture, usually on the second or third or may be delayed until the fifth or sixth day.

The writer has seen it appear in twenty-four hours, following a severe stab wound in the abdomen. Many patients on the verge of an outbreak of delirium tremens will deny positively and firmly that they have drunk any alcohol; when this is in marked contrast to the physical evidences of alcoholic indulgence it should always warn one of the imminence of a severe outbreak.

Many patients, when they begin to have insomnia and disturbed dreams at night, realize their condition and come to the hospital for treatment. They still know that the hallucinations of sight or hearing are dreams and explain this carefully. Some are still able to focus their attention on other matters and avoid the hallucinations that appear when dropping to sleep. One patient explained to me that he would read most of the night in order to avoid the family of skunks that came and played about his legs. They are often free from hallucinations during the daytime, and after a few nights of disturbed slumber improve, and this abortive form of delirium tremens passes over. In other patients, after the premonitory symptoms, the intensity suddenly increases and they are brought to the hospital in a furious and active delirium. This is usually connected with their daily occupation and they show no fear of what they see but are furiously belligerent; their attention can easily be obtained and they will explain minutely what they see, and demand to have their orders executed and explain logically why they wish to have this done. These patients, after a hypnotic and a night's rest, will clear up absolutely and by next morning remember shamefacedly what they had done. The delirium usually does not return.

The majority of patients, when the delirium is fully developed, appear severely ill with a disturbed and anxious countenance or their expression may be one of indifference; the face is congested, often slightly cyanotic and covered with sweat; they are restless, wandering about, busily twisting and turning, listening to imaginary voices and sounds. If in bed, they frequently attempt to leave it, pull and pick at the bedclothes, jump up, attempt to rush from the room and frequently hurl themselves against the walls to escape imaginary objects or push against the walls to prevent their falling in and crushing them. They fail to notice objects in their way and are indifferent to severe injuries. The gait is uncertain from the muscular tremor, which is noticeable in their hands with every movement, and often extends into the tongue and the muscles of the face. Their speech is trembling and stammering, or they blurt out expressions in short, sharp sentences. Some hardly speak at all; others shriek out questions and answer them, angrily discussing something and frequently scolding and cursing imaginary bystanders. The pulse is full, bounding, and increased in frequency in the young and vigorous individuals and in the elderly or weak it often increases in frequency but is soft and weak. The respirations are increased, the tongue is usually coated, but when the digestion remains good it is often clean, bright red, and glazed; the temperature, as a rule, is near normal. By speaking sharply to the patient, his attention may be arrested for a moment and he may answer the question correctly. Ordinarily the ideas of his personality and past remain clear; but he has false ideas regarding his

environment, the purpose for which he is in the hospital, the length of time that he has been there, and the individuals around him.

Hallucinations of sight predominate and it is usually an occupation delirium; for example, an hostler saw innumerable numbers of wagon wheels rolling at him; the circus man saw elephants jutting out into the room, which crowded him, although they did not terrify him; the teamster usually drives horses and it is often a noticeable fact that as long as the horses obey his orders, he is not terrified, but if the horses back against his orders and he is unable to control them, there is terror and the intensity of this is often a fair criterion of the severity of the delirium. The animal or menagerie delirium is common and the patients may see well-known animals, or fantastic beasts, and various horrid forms of monsters, or there may be disgusting insects, crabs, and snakes of various forms. These animals or imaginary monsters are not seen singly but usually in vast numbers. At times the hallucinations are pleasant and the room is filled with beautiful pictures or angels are talking to them. Sometimes the visions take on a sexual type. Various paresthesias of the skin cause hallucinations of worms or spiders crawling on them. Specks on the walls or on the bedclothes may be mistaken for various animals or vermin. Scratches, furuncles, or injuries and the like may be mistaken for the bites of animals or for wounds given in attempts to murder them. The hallucinations of hearing consist of various noises, as the ringing of bells, crying of children, shrieks of people in distress, and volleys of musketry, or they are cursed and jeered at, or they hear their family outside the door conspiring to kill them or whispering and making plans to mutilate them, the mutilations often taking the sexual characteristics. Rarely there are hallucinations of smell, and they imagine that the house is on fire, or that ill-smelling gases are being injected through the key-hole. The hallucinations of taste are also rare, but they may imagine that their food is covered with disgusting substances or that poison is being placed in it. Hypochondriacal illusions from sensations in the intestines, stomach, bladder, etc., do not occur; when present they give cause for the suspicion of other mental diseases. Muscle and temperature sense are normal.

The mental processes are of a peculiar nature; there is no diminution in general in the sharpness of perception of the sense organs; the ability to recognize objects seems intact. Some authors believe that these patients are unable to obtain any sharp, clear impressions and explain the misinterpretation of noises, etc., as due to disturbances of apprehension; these become very apparent when the patients attempt to read, when instead of correct sentences there is a senseless series of words and sound associations which is especially noticeable when the type is small and indistinct; sometimes there is no relation between the reading and the subject matter. Bonhoeffer's explanation that the inability to read accurately is due to disturbances of attention seems nearer the truth. He believes that the paraphasia and paralexia are closely related to the processes of physiological inattention. The power of attention under special conditions in delirium tremens can for a short space of time attain the sharpness of that in healthy persons, but the ability to

hold the attention is quite different. The more complicated the mental work, the greater are the demands on the attention and the greater the tendency to paralexia. With a sharp strain on the attention for the purpose of holding fast this maximum accuracy of any sensory region, a transitory normal value is attained, but there appears an increased tendency to hallucinations in the sensory regions. If the attention is held at a middle level but still so strongly taxed that the patient must talk with and give answers to the examiner, the hallucinations become rarer. The disturbance then records itself in a tendency to mix up words and ideas similar to the physiological inattention. There exists a persistent tendency to sink to a still lower level of attention.

Closely allied to changes in the ability of fixing the attention, is the train of thought by which stimuli through the various sense organs bring about the final conception of the object. Simple pictures presented to a delirious patient, or familiar sounds, may be often correctly recognized and designated, but in severe cases these are often misunderstood and cause hallucinations. At times the misinterpretation of pictures would lead one to believe that lack of color perception played a certain rôle. It is very characteristic for the misinterpretations to influence and lead to illusions through internal rather than through external similarity, as, for instance, the patient, looking at a picture of a bird declares that it is a bird's nest. The final conception of the object lacks intensity and the ideas which come into consciousness are those which belong to associated related ideas. These patients are particularly susceptible to suggestion; this, however, extends only to the regions of sense from which the hallucinations come, and it is therefore strongest in the optic and in the auditory senses, but often fails with touch, and seems to completely fail in the regions of smell and taste. Suggestion can also affect the hallucinations concerning their external environment, especially as to occurrences in the recent past, but has no effect whatever upon the events of their early life. These patients have no idea of the passage of time and the duration of their illness is usually wrongly given; the day, the week, the year, are ordinarily misstated. The power of retention is much diminished and memory of objects seen is defective, this being strongest at the height of the delirium but also clearly apparent when the delirium has nearly ceased. The power to combine thoughts is distinctly in abeyance; this is clearly seen when one permits a patient to read, for he will read spontaneously the greatest nonsense without exerting the slightest critical faculty.

One of the most marked peculiarities is the misconception of place and environment and, up to a certain degree, of time; they have entirely lost their orientation. They are able to remember and describe clearly the contents of their own room; one can sometimes make them clearly appreciate the objects which compose their present environment, and yet they will be absolutely unable to appreciate that they are not in their own room and in a hospital. Their occupation, former life, and all ideas that relate to their personality are unaffected. Ideas of grandeur do not occur in true delirium tremens; if they appear, it is the complication of some other psychosis. The emotional attitude depends

largely upon the character of the hallucinations and illusions; they may be happy or fearful, they are more often anxious and fearful, and these may rapidly replace each other from time to time. The feeling of anxiety is almost never absent from the beginning; it is first seen as an oppression in the chest or as an external restlessness; this seems to be particularly prominent in patients with dyspnœa. During the height of the delirium the anxiety often diminishes and gives place to a euphoria, so that the patient becomes indifferent even to the hallucinations which previously terrified him, and he may even be amused at the external phantasies that are being worked out and played before him. The motor impulses are in most patients very pronounced. As many patients show occupation hallucinations in some degree, so their movements usually correspond with these. The impulse to speak often corresponds with these movements, but frequently patients will be busily moving about for hours, or lying in bed actively busy in many ways, without saying a word.

The *tremor* from which the disease really takes its name is apart from the motor impulse just described and differs from the ordinary tremor in chronic alcoholism only in its intensity and in the greater distribution. It may be so marked in delirium tremens that the patients totter and are unable to hold themselves erect, or, when lying in bed and suddenly spoken to, it may assume such convulsive intensity as to throw them off the bed. It persists even when the patients are at rest, although by movement there is a great intention increase. The tongue trembles strongly when thrust out and this often causes intense tremor in the muscles of the face. The eye muscles remain free from tremor and the head, as a rule, only takes part slightly. In slight degrees it can be controlled when the fingers are held closely together, but becomes distinctly apparent when they are stretched wide apart. In convalescents, after the tremor has disappeared, it can be felt in the interossei muscles when these are taken between the index finger and the thumb. The speech often shows a distinct ataxia; besides trembling of the voice, there is often also a stumbling over syllables and words, and mispronunciation, which is as apparent in voluntary speech as it is in reading aloud. The handwriting shows some disturbance; besides the tremor, words and syllables are left out and an inability to follow straight lines with the tumbling of words above or below each other is seen. Sometimes in the morning tremor of drunkards, a glass of alcohol will steady the hand, so that the handwriting becomes clearer.

There is a great tendency to sweating and often the slightest exertion brings on profuse perspiration. The tendon reflexes are, as a rule, not changed. The sleeplessness continues throughout the entire extent of the delirium and ceases as the delirious period comes to an end. The temperature usually rests near the normal line during the delirium; it is raised in some cases, usually not above 101° , except in patients in whom the motor impulses are very intense and there is incessant muscular movement. Under these conditions temperatures of 103° and 104° are not uncommon; temperatures of 105° from these causes are of serious prognostic significance. During the summer months, in periods of great

heat in New York, it is noticeable that febrile delirium is most common when the motor excitement is very intense. The patient may pass into a condition of heat stroke, the temperature may rise to 108° F., and the patient die.

During the delirium the pulse runs from 80 to 110 when the heart muscle is in fair condition. With much emotion or intense motor activity, the pulse is correspondingly increased; its quality is usually soft. Constipation is the rule. Several German observers lay great stress upon the frequency of albumin in the urine, with no other signs of nephritis, which disappears after the delirium has ceased. Albumin appears in about half the cases in the beginning of the delirium, and in others on the second and third day, it is transitory and may cease a day or so before the delirium or it may last a day or two after the cessation, but, as a rule, is small in amount. Leipmann found albumoses in about 15 per cent. of the delirious patients, and toward the end of the delirium they are found in addition to the albumin. Bonhoeffer quotes Elsholz as having found an increase in the polynuclear leukocytes and a diminishing of the mononuclear, but no leukocytosis. In cases of severe delirium the eosinophiles were absent.

The duration of an attack in mild cases is two or three days; it averages probably three to five days and may continue for eight or ten days. The cessation of the delirium usually follows a deep sleep which may last uninterruptedly for twelve to thirty hours. Some authors describe this sleep as coming on in the midst of the delirium, but it is usually preceded by a period of weariness and relative quiet. When the patient awakens from the critical sleep he is sensible, the hallucinations have gone, and his orientation is usually complete; his mental condition, however, is not fully recovered; the power of retention is diminished and the ability to combine thoughts is distinctly diminished for a few days. The memory of the recent illness is never complete, but it is accurate for the essentials; it is very rare that complete forgetfulness occurs. As to the duration of his illness, the patient rarely has an accurate idea, deeming the time shorter than it really was. In general the emotional and fantastic occurrences are better remembered than the ordinary ones, but after four or five days even these lose their distinctness. Often for several days therapeutic measures, which were necessary during the stage of delirium, are remembered and still misunderstood as forms of persecution. In old alcoholics who have had previous attacks of delirium, there is at times a certain appreciation of the disease during the entire delirium and they also show a corresponding clearness as to its occurrences. On the other hand, these same patients are very prone to consider hallucinations as realities and retain these misapprehensions for a long period. In not a few patients there is a recrudescence of the delirium for a few nights, while remaining free of it during the day; any unusual excitement producing mental exhaustion may often during the daytime bring back some of the hallucinations.

Meningeal Symptoms, Serous Meningitis, "Wet Brain."—In all forms of alcoholism, but especially in acute and chronic delirium, a condition sometimes develops which has only recently attracted the

attention that it merits. It has often been called alcoholic meningitis or serous meningitis, which is a misnomer, for there is no true inflammatory process and the excessive amount of fluid in the peri-arachnoid space is a transudate and not an exudate.

Stillman has made an extensive study of this condition and has proved that the fluid in the pial oedema of most chronic alcoholics is not *per se* an oedema of the pathological process but in every instance represents the reciprocal of brain shrinkage. He further shows that this fluid produces *per se* no symptoms and that the thickening of the meninges takes place chiefly in the arachnoid and is not to be regarded as representing a true inflammatory process. Although this pial oedema is much more common in alcoholics than in any other condition, it has no other significance than that of brain shrinkage. The post-delirious stupor which intervenes following the acute or chronic delirium of alcoholics is not due, as has generally been supposed, to intracranial pressure and the presence of the increased oedematous condition of either the meninges or the brain, but must in all probability be due to cerebral toxemia produced by the chronic alcoholism or in some way connected with the exhaustion supervening from this condition. It occurs with relative equal frequency in men and women. It usually follows an attack of delirium tremens, though it may develop in any chronic alcoholic after an injury or after a debauch without previous delirium. When it follows delirium tremens the patient, after a few days of delirium, sinks slowly into a semicoma. As Stillman points out, the first symptom to attract attention is that the delirium has changed from an active, noisy type into a low, muttering variety in which the facial expression has changed, the heightened color has given place to a gray pallor and almost cadaveric immobility. The patient usually lies flat on his back with legs extended, the head thrown slightly back, and the unobserving glance directed toward the ceiling toward which the hands reach in a rather characteristic manner, suggestive of rope climbing. They are seldom still for more than a few seconds and exhibit the weak, wide tremor of cerebral irritation. Their mumbling articulation is in counterdistinction to the muttering of other types of delirium in which the spoken words are more sharply defined, but in this form the labials seem absent as if the patients were unable to use their lips.

The patient is aroused with difficulty, though he still will take food. The pulse is rapid, the temperature remains normal or is slightly raised, but seldom over a degree. The pupils are usually diminished in size. The skin is hyperesthetic, and pressure on the muscles of the arms and legs and over the abdomen causes pain. Conjunctivitis and keratitis often develop. In some patients the condition slowly progresses for several days, in others the effusion increases rapidly, and they sink into a more profound coma from which they cannot be aroused. The arms and legs become stiff, the reflexes are all exaggerated, the neck is stiff, slightly retracted, and attempts to move it cause pain. The abdomen is retracted and the skin and muscles are still hyperesthetic. The lids are closed; the pupils are contracted and react slowly if at all. The tongue is dry and brown, and there is usually incontinence of feces

and urine. The pulse is frequent and feeble, and the extremities are cold. He may continue in this condition for several days and gradually die, or improvement may begin slowly, the mind becomes clearer, the neck less rigid, the hyperesthesia diminishes, and recovery follows. Often three or four weeks are required before the patient is really convalescent. Pneumonia, especially inhalation pneumonia, is apt to develop; the temperature may rise to 101° to 104° F., and the patient dies. In 709 cases of delirium in Bellevue Hospital, New York, this condition developed in 108 instances (15 per cent.); of these, 37 recovered and 71 died—a mortality of 65.7 per cent. The prognosis is always grave when the coma and rigidity have become well developed. Dana gives the stiffness of the neck as a useful prognostic criterion; if the patient has not a stiff neck he will recover, but when it comes on, the patient dies.

Prognosis.—The outlook in delirium tremens depends greatly upon whether it is complicated by trauma or infectious diseases, especially pneumonia. In 709 cases of delirium occurring in Bellevue Hospital, there were 143 deaths or about 20 per cent. Of these, 61 died of pneumonia, about 36 per cent. There were 125 cases of pneumonia in these 709 patients, and after deducting these in the 584 remaining, the death-rate was about 14 per cent. Of the 125 cases of pneumonia, 64 recovered, leaving a mortality of 48.8 per cent. In uncomplicated attacks in young individuals the prognosis is fairly good. In the beginning of any attack a guarded prognosis should be given. If the delirium develops into a severe form and the motor symptoms are very intense, the prognosis is correspondingly grave. The so-called moderate drinkers, who develop delirium tremens after trauma, have a bad prognosis—in the experience of the writer about 50 per cent. die. In true delirium tremens, as differentiated from acute alcoholic hallucinosis, the tendency to suicide is unusual. The changing character of the delirium prevents the fulfilment of any transitory morbid train of thought. The premonitory stage, when there is great intensity of painful emotions, anxiety, and unrest, is the time in which the tendency to suicide is most apt to develop. It is difficult in these early stages to say whether the patient is developing true delirium tremens or an acute alcoholic hallucinosis, so that the statement that in true delirium tremens suicide is rare, remains true.

Treatment.—We must realize that there is no specific and treat it symptomatically. Most of these patients have been subsisting, often for long periods, on alcohol, with little or no food. The danger is not in the delirium but in the diseased condition of the heart muscle and vessels and that the gastric mucosa is in such a condition that substances given by mouth may remain unabsorbed for hours, and then suddenly be absorbed and the system be overwhelmed by accumulated doses. This has seemed to the writer the reason of the increased death-rate under the old digitalis treatment. Many drugs have been vaunted, but in a disease in which the critical cessation comes on with sleep, it is really impossible to say whether the sleep was coincident with the crisis or whether there was really any cause and effect in the administration of the given hypnotic. The question whether alcohol should be

withdrawn at once or continued is still debated. It is the writer's belief, after trying both methods, basing his judgment on the treatment of several thousand patients by each, that alcohol should be absolutely withdrawn in young and vigorous patients but in the weak and elderly it should be rapidly reduced. First and foremost, all these patients must be treated from the standpoint of those having a degenerated heart muscle and they therefore should be stimulated with strychnia (gr. $\frac{1}{60}$ to $\frac{1}{30}$, gm. 0.001 to 0.002) every four hours or oftener, or by caffeine or camphor, and these are best given hypodermically. Strong coffee or tea can be given in mild cases instead of the pure caffeine. The patient must be given a vigorous purgative, such as compound cathartic pills or calomel. In young, vigorous adults, without any appreciable change in their arteries, who have recently been drinking, an emetic such as copper or zinc sulphate is often an advantage. This should never be given in elderly persons or in those who appear old for their age.

In mild and abortive attacks paraldehyde (℥j to ℥ij, 4 to 8 cc.) repeated if necessary in an hour, is all that is necessary to cause sleep from which the patients frequently awaken either clear-headed or with their delirium lessened. In the severer cases, the paraldehyde may be given in double this dosage. Other hypnotics, such as sulphonal, trional, etc., have in the hands of the writer usually failed utterly except in the mildest cases. Opium should be resorted to only as a last resort and is especially contraindicated with pronounced arteriosclerosis. Hyoscine (gr. $\frac{1}{125}$, gm. 0.0005) and morphine (gr. $\frac{1}{6}$ to $\frac{1}{4}$, gm. 0.01 to 0.015) hypodermically should only be given to young and vigorous individuals in whom the motor symptoms are marked. Hyoscine alone tends to increase the delirium, especially in women. Often in the severest cases a mixture of hyoscine, (gr. $\frac{1}{100}$, gm. 0.0006) with apomorphine (gr. $\frac{1}{10}$, gm. 0.006) and strychnia (gr. $\frac{1}{30}$, gm. 0.002) will quiet them and give at least a few hours rest. Bromides are insufficient and in the hands of the writer have been practically useless. Chloral is one of the best drugs when properly administered; small doses are useless. Lancereaux recommends thirty to sixty grain doses (gm. 2 to 4); the combination of chloral and morphine is especially advantageous in that smaller doses of each can be given and the mixture is more effective than either singly. The mixture of morphine (gr. $\frac{1}{8}$, gm. 0.008), chloral (gr. 15 to 30, gm. 1 to 2) with tincture of hyoscyamus (℥ss, 2 cc.), tincture of ginger (℥x, cc. 0.6), and tincture of capsicum (℥ij, cc. 0.2), and water to ℥ss (cc. 15), is very effective and can be repeated at the end of an hour. These hypnotics, while causing sleep, do not necessarily cut short the delirium, but after a sleep of some hours the delirium is often quieter and there is the further advantage of rest for the heart. Of late years the writer has used ergot hypodermically in Livingston's solution, which is as follows: One dram of the solid extract of ergot is dissolved in an ounce of sterile water and three drops of chloroform and three grains of chloretone are added, and the solution filtered; this is sterile and should be given straight into the muscles in the gluteal region or in the deltoid. It should never be given subcutaneously; if carelessly given, it produces painful spots. The administration of thirty drops of this solution, hypodermically,

every two to four hours, reduces the dilated bloodvessels, lessens the various congestions, and brings about a better equilibrium of the circulation. After it, there is a distinct tendency to a quieter delirium and less need of restraint. The writer has never seen symptoms of ergotism although thirty minims of this solution were given every two hours for ten days or longer. As soon as patients awake they must be given food, best in the form of milk or milk and eggs. This should be given regularly every two or three hours during the delirium but if asleep they should not be awakened for any reason.

The treatment for the "wet brain" condition should be begun as soon as it is suspected. Strychnia, gr. $\frac{1}{60}$ to $\frac{1}{30}$, and ergot, 30 minims, both hypodermically, should be given every two hours, and caffeine and camphor are also of use. The patient should be carefully fed every two hours with milk, broth, and eggs, and thorough purging is advisable. Alcohol seems to increase the effusion and should not be given. During convalescence, however, a little alcohol in the form of egg-nog two or three times a day for a few days is often of benefit.

Bonhoeffer recommends that delirious patients should be placed for several hours in a warm bath at 95° to 97° F., and that an attendant should sit beside them so that when they attempt to get out of the bath, their attention can be diverted. He also recommends that one or two attendants should sit beside the delirious patients and keep them in bed, which is excellent treatment where there are many attendants and few patients, but where the reverse is true in a large, active service, restraint is often necessary. There is no question that these patients should be confined to bed through the entire delirious stage, as in the wilder delirium it is often necessary to restrain them by a sheet tied around their ankles and then tied to the foot of the bed, and by another sheet which goes from the bed up over one shoulder, down through the axilla, across the back to the opposite axilla, up across the shoulder, back to the bed; the wrists, when necessary, can be restrained by a muslin bandage wrapped around over cotton wool which thus prevents abrasions and holds them firmly; sometimes a folded sheet stretched across is sufficient to hold them in bed. The hot, stiff, jacket is essentially bad, as it rigidly binds the patient and prevents the radiation of heat. The question of the isolation of these patients and the permitting them to wander about in a padded room is often brought up; young vigorous persons can be so treated for a few hours, provided the tremor is not too great and the delirium not so violent that they will do themselves injury. We have, moreover, always to consider sudden collapse, and the degree of cardiac degeneration cannot be accurately judged, so that, on the whole, it would seem better to keep all patients in bed during their delirium and not to isolate them. In hospitals, the patients, although in open wards, are but little disturbed by their fellows, especially during their delirium, because they are too much occupied with their own hallucinations to pay attention to the disturbances caused by others.

During convalescence, stomachics, such as capsicum, nux vomica, and ginger, are useful. In the febrile cases a bath is often necessary or the patients are placed on a rubber blanket in bed, and cold water is

slapped forcibly upon them from a whisk broom; the impact of the water takes the place of the physical rubbing in the bath. Warm packs have been recommended, but often the resistance made by the patient, and the excitement produced, do more harm than good. Usually eight or ten days after the patient has recovered from his delirium he is fit to go out, and in hospitals his treatment here ceases. If possible, they should go to some place where they may live in the open air with good food and have moderate outdoor exercise. Total abstinence from alcohol is their only hope for future health; for this reason it is inadvisable to give any medicine with alcohol in it.

Acute Hallucinosis.—Acute hallucinosis of drunkards is sometimes called acute alcoholic hallucinosis, acute paranoia, or acute persecutory insanity. It is closely allied to delirium tremens, and there are cases which seem more like connecting links than belonging clearly to either one. The patients are usually younger than in delirium tremens and belong to the better educated classes, while delirium tremens is most common among those who perform manual labor. The tendency of this form of alcoholic psychosis to develop as a concomitant symptom of trauma, pneumonia, and other acute diseases is not so great as delirium tremens. Acute gastric disturbances are the most commonly observed physical ailments connected with it, and it frequently follows fright and intense anger. One attack of delirium has taken the form of delirium tremens and another the form of acute hallucinosis.

Symptoms.—These patients show a predominance of the acoustic type of hallucination, although optic and tactile hallucinations are not infrequently present, but not as prominently as in delirium tremens. There is, in the beginning, the same irritability, easily excited condition, restlessness, and undefined dread as in delirium tremens, but they often show a peculiar sensitiveness to ordinary noises; they are sleepless, their dreams are bad, and they start in their sleep, terrified by an unknown something. This unstable condition may persist for days and then become somewhat better, and a further debauch cause all the symptoms to return and go on rapidly into a full development of the complete psychosis. They are often troubled, at first, with noises in the ears, which develop into the hallucinations of singing, music, shooting, screaming, etc.; finally they are persistently followed by definite voices, which hold their attention constantly at high tension and compel their undivided attention. Frequently they are brought into the hospital by the police because they have fled from the persecution of these voices, or they go to their rooms and refuse to come out or allow anyone to approach. In this early stage, suicide is very common, especially in those in whom the terror is highly developed. The voices are sharply localized, they accompany the patient from behind, creep up at him out of the floor, come to him from a hole in the wall, or seem to be persistently telephoning to him. When he strives to sleep, they come up out of the pillow, from under the bed, and they follow his every movement. These voices have a definite character; they may be the voice of a man, woman, or child, or the clearly recognized voice of some friend, or they may be unmistakably not human, or the voices may seem human and speak in a foreign

tongue. The rhythmical character of the hallucinations is quite common and sometimes the patient hears constant repetitions of the last word spoken to him, or the last thought which he has had. As he goes into the street the auditory hallucinations, as in delirium tremens, take on the abusive character, and he hears himself called by name with various epithets added, or accused of various criminal acts. Not infrequently, the patient hears every thought as it occurs to him, spoken out aloud, and he declares that he knows the very spot of the tongue out of which his thoughts are loudly spoken; frequently he hears every movement he makes commented upon by the voices.

Optic hallucinations are present but take a subordinate position; they frequently occur at night and often are the outlandish, terrifying, mixed-up pictures seen in delirium tremens. The sense of touch is less often involved and hallucinations of taste and smell are absent. These patients are not usually disturbed by sensations from the internal viscera; sometimes, however, they seem to form an unimportant part of the hallucinations. When these last sensory regions give predominant hallucinations, there is always a strong suspicion that we are not dealing with a pure alcoholic psychosis, but with a more serious condition. Frequently there is a suspiciously disturbing misconception of all acts that are performed by others in his presence; he believes that people moving in the street are running together to discuss him; he is suspicious of the patients in the hospital, believes that the motions made by the nurse in handing him his food prove he is about to be poisoned, and misinterprets all therapeutic measures. The idea of persecution does not go farther back than the recent past; his persecutory system is superficial, changes during the disease, and often develops suddenly; ideas of grandeur are sometimes present.

Consciousness is not clouded, and they retain their power to combine thought and their powers of retention. Disturbances in the process of thought, as in delirium tremens, are not present. Most authors seem to believe that their orientation for place, as a rule, remains intact. In the patients who show a type of the disease tending toward the clinical picture of delirium tremens, there is sometimes disorientation especially in the beginning of the attack. Tremor of the hands and tongue, and gastritis, are usually present; the symptoms of neuritis are not uncommon, and other disturbances of chronic alcoholism, such as a tendency to perspire freely, etc., are common, although they are usually less marked than in delirium tremens, perhaps because this psychosis more often occurs in younger individuals. The duration of this disease varies from a few days to weeks. Rarely does it continue more than two months, according to Bonhoeffer. As the patients improve, there are periods in which they seem to be free from hallucinations. Finally, the voices in their ears are recognized as such and no longer produce the hallucinations. The various erroneous impressions improve coincidentally with the disappearance of the voices. Wernicke believes, however, that these patients go through a paranoiac stage in some hallucinations in which their systematized illusions persist; however this may be, this stage is evidently of short duration, because the accurate appreciation

of their psychic condition often occurs with an astonishing rapidity. They remember their hallucinations and are often proud to write a description of them. Sometimes these patient go from these acute hallucinatory stages into a condition of chronic delirium. There are no known pathological lesions characteristic of this psychosis.

Prognosis.—The prognosis as to life, if they are put into an institution, is good, but if they go through the early stages uncared for, the danger of suicide is great. The liability to death from intercurrent disease is not great, and the more they tend in their clinical picture toward the transition type of delirium tremens, the shorter seems to be the duration. Ideas of grandeur seem to tend to a somewhat longer duration. If the paranoiac condition has been prominent, continued alcoholic indulgence is liable to produce permanent insanity.

Diagnosis.—Bonhoeffer gives the following differential diagnosis between the acute hallucinosis and delirium tremens: The acoustic region dominates in the hallucinations in hallucinosis, the optic and tactile in delirium tremens; in hallucinosis orientation is retained, in delirium tremens it is lost; in hallucinosis the morbid occurrences are systematized and the patient has the illusions concerning his relations with others; both these conditions are lacking in delirium tremens; the disturbances of retention and the disturbances of memory dependent thereon concerning time and succession, the confabulation, the disturbances of attention and the power to combine thought are lacking in hallucinosis or at least are scarcely apparent. In spite of these differences, transitional forms occur which are likely to cause errors in diagnosis.

Treatment.—This is the same as for acute insanity; the tendency to suicide must never be forgotten and isolation is contra-indicated. They should be kept in bed during the delirium; hypnotics should be given to produce sleep as in delirium tremens; especial attention should be paid to their digestion and to frequent feeding; cathartics will usually be necessary. Bonhoeffer recommends frequent warm baths for these patients. One can often impress on them after their recovery, with much better hope of intelligent appreciation, the necessity of total abstinence from alcohol.

Chronic Alcoholism.—Many of the forms of chronic alcoholism are described under other diseases, such as cirrhosis of the liver, arteriosclerosis, etc., for here, as in all forms of alcoholism, the idiosyncrasies of the patient are important factors and the kind and amount of the alcohol used modify the clinical picture. The amount of alcohol which, consumed daily, will produce the lesions and symptoms of chronic alcoholism varies with the individual; most men who partake of moderate doses dilute their alcohol with large amounts of water and the effect produced is less than when the fluids are taken in concentrated forms. Many men take moderate amounts of whisky through long years with apparently no serious effects; many others partake of moderate amounts with their meals and seem to be benefited, and not injured, thereby. It is a noticeable fact that the wine connoisseur rarely becomes a drunkard. As soon as an individual begins to take alcohol for the effect produced, he is in danger of continuing the practice and becoming more and more

tolerant; he requires more to produce the desired effect and soon partakes of amounts that necessarily must injure the organism.

When once the condition of chronic alcoholism is developed, the first symptoms are those of weakening of the will and blunting of the moral nature; the patients become untidy and slovenly in their personal habits; are careless in their ways of doing things; forgetful of their promises and engagements; lose their sense of responsibility to the community as citizens, and to care and provide for their families; their judgment and memory fail progressively. They become more and more selfish and self-centred, increasingly incompetent through forgetfulness and carelessness, and to cover up their shortcomings are at first prone to make excuses which are followed by actual lies to escape the responsibility of their misdeeds. They lose their sense of shame, and although, while the remnants of their better nature remain, they may promise to give up drinking, if they break this promise, they make excuses and seem to be shameless regarding it. They are irritable, touchy, and liable, from slight causes, to intense fits of anger during which they will cruelly punish their children for slight offences; they may abusively scold their wives and families on the slightest pretext or brutally maltreat them. With the weakness of will there is a conceited self-complacency which causes them to declare that they can stop drinking at any time if they wish, and yet when pinned down to the necessity for so doing, they have a never-ending series of excuses to avoid doing it. There is a very characteristic suspicion in the minds of these patients of the faithlessness of their wives, which, according to Kraft-Ebing, is produced by a failing sexual desire and a rapidly occurring impotence. Usually this does not express itself further than in contemptible and vicious vituperations; it may cause, however, in fits of drunkenness, actual bodily harm and even murder of an innocent wife or of the children, as suspected accomplices of their mother. These evidences of mental degeneration may continue through years, and the patient finally sink into early senile dementia, for unfortunately a degenerated intellect does not necessarily produce death, and as long as the heart and arteries hold out, many degenerated alcoholics continue to live, a burden and nuisance to the community. They usually die before alcoholic dementia is fully developed, because of the liability to trauma and intercurrent infectious diseases, or during an attack of delirium tremens or other psychosis, or from visceral degenerations, or cerebral hemorrhage.

Dipsomania or Periodic Inebriety.—In some individuals alcoholism exhibits itself in a form of periodic crises, the dipsomania or periodic inebriety of some authors. This is not a single condition but is the expression of periodic outbreaks of drunkenness due to several causes. In some patients it is the intense exacerbation of a really persistent alcoholism, and although they claim not to be drinking, between times they really are drinking little by little until they are sufficiently poisoned to go to the full excess of a spree. Others are really abstinent between outbreaks. In some this drinking is but the expression of a recurrent maniac depressive psychosis, or other psychosis, and they only drink when these attacks of psychosis occur. These are the true dipsomaniacs.

Others believe that these attacks are related to periodic epileptic explosions, but the more one sees of these patients the less often does this explanation seem true. In some it seems to be the expression of faulty nutrition or an attack similar to migraine, and often the attacks are preceded by mental depression, restlessness, irritability, headache, anorexia, sleeplessness, and precordial anxiety, and the desire to drink becomes irresistible. Some patients will mix various disgusting substances in their beverages hoping thus to stop the craving. The periodicity varies from weeks to months or even a year or more. In some men regular recurring tasks or business stresses bring them on; in some women the menstrual periods seem to be the cause. In some patients, if protected for some hours or days, the craving passes away and they are safe until the next attack. There are some patients who drink to obliterate compelling emotions in consciousness. Either this emotion may be in the subconscious and unknown to them, or it may simply be the deliberate or irresistible impulse to obliterate something they cannot or will not face in consciousness. Many patients in whom the attack seems to be without exciting cause, if questioned closely, are found to be great tobacco smokers and the cause of their outbreak is really a recurrent poisoning by tobacco. Usually the history is that they smoke, especially the cigarette smokers, incessantly and to excess. This finally makes them nervous. They then smoke more to quiet their nervousness until finally they seek another narcotic to quiet them and naturally turn to alcohol. They are abnormally sensitive to this last narcotic, and often after a single drink will not be sober, and then they will drink to full excess. When they become sober they cease to smoke and drink, then gradually begin smoking and the cycle is repeated. This, in the writer's experience, forms a very large class of the periodic inebriates whose periods are classified as occurring without apparent cause. Sometimes patients in the beginning dipsomaniac attacks will only drink to drunkenness, cease of their own volition and later their debauch goes on until they are forced to cease under restraint unless the periodic habit is broken. In the majority the periods between attacks shorten until they finally develop into chronic alcoholism with no periodicity. During any debauch they may develop an attack of delirium tremens or any form of alcoholic psychosis.

For the recurrent attacks of mental depressive psychosis, institutional care until the period is past is the only treatment. For those poisoned by tobacco the only treatment is to stop smoking absolutely, as this is the only method by which the vicious circle can be broken. Among those suffering with the compelling impulses the employment of psychoanalysis and the working out of their individual problem is the only method of solving their difficulties. With those suffering the attacks similar to migraine the solution is one of disturbed metabolism and the problem must be worked out from this standpoint.

Alcoholic Trance, Automatism, or Pathological Drunkenness.—In psychopathic, hysterical, or epileptic patients, or following traumatic injuries to the skull, or after sunstroke, alcohol produces disturbances of consciousness which deviate greatly from the ordinary sequences. The

same conditions are seen in those who have been injured through the excessive use of alcohol; one of the simplest expressions of this condition is that in which the patients, after much smaller amounts of alcohol than formerly, become drunk and are absolutely oblivious next day to everything that occurs. After the first or second drink they may seem to their friends simply to have been drinking and not more than usual under the influence of alcohol, or they may in slightly more pronounced cases, completely lose their orientation, misinterpret entirely their environment, and show an ugly disposition, which was foreign to them, with evidences of a high degree of emotional anxiety. More pronounced examples of alcoholic automatism are those in which the patient may start off on a prolonged debauch and at the end wake up in some far-away city with all occurrences from the time he began until coming to himself quite forgotten. The amnesia is usually complete; sometimes there are faint recollections that he has been recently in certain places; for instance, one patient of the writer remembered taking a drink in Boston and ten days later, having gone through a five days' attack of delirium tremens in Bellevue Hospital, came to himself with complete amnesia of everything which had occurred during the ten days; another who was drinking and sociably chatting with a friend, with no intention of taking enough alcohol to disturb his sobriety, came to himself five days later while ascending the stairs of a station of an elevated road, and was unable to remember any occurrences of those five days except that he had been in some bath establishment. This man was not an alcoholic, and filled a responsible position, although some years previously he had drunk to excess. Other patients, after a single drink or during a debauch, have been known to start off on long journeys and come to themselves on board a railroad train or a steamer. Others have been known to conduct complicated business transactions shrewdly and successfully, to go into court and conduct successfully a long trial, ending with a prolonged charge to the jury, come home and write out a long legal document concerning the case with perfect clearness and conciseness, and yet when consciousness returned, the amnesia was complete. In some this will occur but once, in others it is of recurrent nature and may be preceded by restlessness and irritability, and after a single drink they regularly go into this state of disassociation of consciousness. In these conditions men have committed forgery, theft, and even murder, without any recollection of them when consciousness returned. Others in this condition of pathological drunkenness murder their children for trivial causes and show no remorse for the act; calmly deliver themselves up and discuss the whole occurrence with no more appreciation or mental disturbance at what they have done than if they had broken a piece of furniture or accidentally injured some animal. Many of these cases belong to medicolegal literature rather than to general medicine. There is no question as to the reality of the total amnesia in these cases, and the responsibility for their acts should be placed in the same category as those of the acutely insane.

Absinthism.—Lancereaux described a special form of chronic alcoholism produced by excessive indulgence in absinthe, various liqueurs, and

aromatic essences. The substances in the absinthe of commerce he divides into two groups, the convulsive and the stupefying; in the first are absinthe, hyssop, and sennel, and in the second annis, angelica, menthe, and marjoram. Absinthe and annis produce the main symptoms. He divides the clinical manifestations into acute, chronic, and hereditary absinthism. The symptoms in acute absinthism come on suddenly; the patient becomes agitated, screams, loses consciousness, and falls; there is a tonic convulsion tending to opisthotonos, followed by a succession of clonic convulsions for twenty or thirty seconds. He then falls back heavily, lies still for a few moments, and regains consciousness. He has no recollection of what has occurred and is astonished that people should be caring for him; this lucid interval is of short duration and is succeeded by similar convulsions lasting for ten or twelve hours. In others the tonic convulsions are followed by clonic convulsions, and the patient throws himself from side to side, grinding his teeth, screaming and foaming at the mouth, trying to bite those around him, striking his chest, and tearing at it. These attacks are of short duration and followed by a period of calm; they end suddenly without cyanosis or coma. A series of such convulsions leaves the patient weary and somewhat stupid. For a day or two he may feel the effect but at the end of this time he is entirely recovered. Acute poisoning of this kind is usually recovered from, although death may occur during the attack.

Chronic Absinthism.—The patient not only suffers from convulsive attacks, but also has neuritis and terrifying hallucinations. Chronic poisoning develops often from an indulgence of less than a year and from amounts of the liqueur which seem inadequate to account for the symptoms on the ground of the alcohol consumed. Women seem to suffer more frequently than men, and especially women below twenty-five years of age. These patients have morning vomiting and marked dizziness; there is marked irritability of the muscles; the eyes are fixed and brilliant; they sweat easily; tremor is marked; and there is extreme hyperalgesia of the body. There is marked hyperesthesia of the skin over the exits of the spinal nerves, diminishing in intensity from below upward; the plantar reflexes are extremely active. Pressure on the abdominal wall is painful, and tickling or touching in the lightest way causes such agony that the patient screams with pain. The tenderest points are in the lower abdomen outside the recti muscles and out into the iliac fossæ. This is accompanied, especially at night, by the most intense pain in the muscles of the legs. In cases of long duration the hyperalgesia is succeeded by analgesia, but the pain, on pressure over the abdomen, chest, or the spinal column, remains almost as intense as at the beginning. These patients are sleepless or when falling to sleep are troubled with terrifying nightmares. Hallucinations of hearing are rare, but have a menacing character and are heard especially during the night; the mental ability, as in all alcoholics, shows weakness. One would judge that they lapsed rapidly into the chronic delirium and not infrequently died in this condition.

Hereditary absinthism is shown in children whose parents are addicted to its use. These children seem to possess an unusually unstable nervous

system and are especially prone to convulsions in infancy, and later to hysterical manifestations, and convulsive seizures. It has been noticed in Bellevue Hospital during the past few years that patients who give a history of drinking absinthe, have shown attacks of convulsions and in the majority there has been marked hyperesthesia and hyperalgesia of the lower extremities; the extreme types have not come under the writer's observation.

Korsakow's Psychosis.—For many years there has been recognized among chronic alcoholics a condition of delirium combined with a polyneuritis; this was finally classed as a distinct and separate psychosis by Korsakow and is now generally called Korsakow's psychosis or syndrome. Mentally there is loss of orientation and a marked defect in the power of retention of new impressions, and loss of memory for the recent past and also for events during various periods of the patient's whole life. There is a strong tendency to confabulation, and to fabrications of the most absurd character and even hallucinations, together with a polyneuritis. This usually occurs in the prime of life and is said by some authors to be more common among women than men, while the statistics of others show a preponderance of men. It usually follows excessive indulgence in alcohol for long periods, although it has occurred as a result of infectious diseases and following poisoning from lead and arsenic. In the majority the psychosis begins with the delirious stage and this may be so marked that at first a diagnosis of delirium tremens is made, but the critical sleep, so characteristic of delirium tremens, is absent and the delirium pursues a protracted course. Acute hallucinations fall into the background and the defects of mental retention with the lack of orientation of time and space, and the foolish babbling, become more pronounced. In other patients, and some claim this to be the usual course, there is a prodromal period during which there are signs of forgetfulness, mental aberrations, and irritability; in some sleeplessness, and in others a stupor from which they are aroused with difficulty. The symptoms of neuritis may precede the delirium or not come on until after it. The length of this prodromal stage varies in different individuals. Bonhoeffer describes a form which develops as a very slow progressive weakness of memory with a sudden exacerbation of disturbance of memory to a definite standpoint. When, however, the characteristic delirium is developed, there is a distinct loss of memory for the recent past; events of their early life may be very clearly remembered, or up to a certain definite time. This amnesia may be complete or there may be curious lapses of memory in which the patient forgets some events and, without any apparent reason, remembers others which occurred during the same period. Many lose all orientation of time or space; especially is the time element defective; they cannot tell whether an event occurred a few moments or a week or several years ago. These gaps of memory are filled in with curious fabrications. This tendency to confabulate and indulge in pseudoreminiscences is very characteristic.

The sense of recognition is much at fault; the patient does not know those about him, or remember his friends or even his nearest relatives.

The attention is easily obtained but kept with difficulty. In the early stages, hallucinations, usually of sight, occur only at night, but as the disease progresses they become more intense and may be present during the day. Optic and tactile hallucinations are most common; these may or may not be terrifying and may assume the fantastic forms seen in acute alcoholic delirium. If the delirious stage comes on early and quickly, these hallucinations are then prominent. The emotional condition varies; some are excited, even simulating a condition of paresis; others are depressed, having the self-accusations seen in melancholia; they are often anxious and disturbed and, later in the disease, are apt to be irritable, quarrelsome, or simply indifferent; in some there is a tendency to be silly and funny; they are at times childish and easily provoked to whining and crying; but in very severe cases they are practically emotionless. They are noticeably lacking in mental initiative and for this reason are very prone to soil themselves; here also weakness of the bodily muscles and the neuritis play a distinct part. They show a distinct power of combination of thought and, as far as the power of retention permits, can reason correctly, especially in some purely intellectual matters.

The symptoms of neuritis are those which accompany polyneuritis; they have the sensory disturbances; there is often an ataxic incoördination; the gait is frequently unstable and they walk with their feet far apart; the regular pains and sensitiveness to touch and muscular weakness are present; the patella reflexes are weak or absent; the joints are lax and the muscles soft; these neuritic symptoms are usually more pronounced in the lower extremities and when the paralysis becomes marked, and atrophy quickly follows; there may then be contractions and permanent deformities. Paralysis of the extensors is more frequent than of the flexors. In very severe cases the upper extremities are involved and one finds a radial, ulnar, or median paralysis. Some individual muscles may escape while others may be paralyzed. The sensory disturbances are variously distributed. One can seldom prove these in single nerves but can simply make out well-marked zones of analgesia and hyperesthesia. Disturbances in the sense of position not infrequently occur; delayed reaction to pain has often been observed; ataxia of the upper extremities is often extremely marked. Severe trophic disturbances may occur. The cranial nerves may be affected. The vagi are not infrequently involved, causing cyanosis, tachycardia, and a peculiar dyspnoea which produces short-breathed speech. Double-sided paralysis of the recurrent laryngeal nerves has been observed, as also disturbances of swallowing and of movement of the tongue. Paralysis of the palate has been seen and paralysis of the external eye muscles, especially of the abducens, is especially frequent. Ptosis is not uncommon. Jelliffe draws attention to the frequency with which pupillary disturbances are present. The true Argyll-Robertson pupil may be present, but the pupils are frequently unequal, the reaction may be slow, or there may be paralysis of accommodation. As a rule, the pupils are very small but there may be marked dilatation, especially in the initial delirium. The pupils may be normal and functionate well. Nystagmus

has been noted and nystagmus-like twitchings are very frequently seen in the last stages.

Wernicke has described a cerebral psychosis with paralysis of the eye muscles which runs an acute and fatal course; this he called poli-encephalitis hemorrhagica superior. This disturbance of the eye muscles went on to complete paralysis. Wernicke believed this to be a separate psychosis and held that it was characteristic for the clinical picture of the disease to have an associated ocular paralysis, a progressive course, and a rapidly fatal ending. Observations have since shown that patients with this group of symptoms do not always die, and several recoveries have been reported. Bonhoeffer concludes that poli-encephalitis hemorrhagica superior is not a separate clinical entity but that the ophthalmoplegia is moderate in certain cases and is an unusually predominating symptom of a general disease, and he further shows that it is nearly related, if not identical, with Korsakow's psychosis.

The *course* is a protracted one; the first stage up to the full development of the mental symptoms continues for some weeks. The neuritis usually shows improvement before the mental symptoms, and in the course of several months may go on to full recovery, although in some there may be permanent atrophy and paralysis. The mental improvement does not run parallel with that of the neuritis but requires a longer time. The powers of retention seem to be the first to improve; then the orientation improves sufficiently for the patients to recognize where they are, and they begin to realize who the persons are with whom they come in contact. The length of time during which this improvement occurs is a varying one; it may take months or years before complete orientation has been obtained. Some authors believe that complete restitution can occur; others deny it. Most observers are unwilling to commit themselves to a definite opinion in this regard. Even after apparent recovery, most patients show some weakness of retention and a forgetfulness which often prevents them taking up their former occupations. They are apt to have a distinct lack of initiative and show irritability and unstable emotions while, unless there is total abstinence from alcohol, they soon revert to their former condition. These patients are very apt to die in the delirious stage and in the severe attacks in which the mental symptoms are very pronounced, death is not often long delayed. There is great tendency to die of intercurrent diseases. The *prognosis* in all recent cases is doubtful, and what is of especial importance, it depends upon the general condition of the patient and the state of his cardiac muscle. In the early stages the severer the delirium the worse the prognosis, and when the neuritis extends to the cranial nerves it is especially unfavorable; thus, when the vagus is involved with tachycardia, dyspnoea, and cyanosis, death very frequently occurs. The prognosis for final recovery, if they have passed the severe stages, should always be given with great reserve. Although they may recover a fair amount of physical vigor and of their former mentality, the chances are always in favor of more or less mental defect remaining.

The *treatment* is in general symptomatic. In the early stages they are best cared for in some institution. In the early months, even in the

milder cases, rest in bed is necessary. The neuritis should be treated as any other polyneuritis. The mental symptoms can only be treated through improvement in the general condition. During the severe delirious stages hypnotics may be necessary; in the later stages the milder hypnotics are sufficient when any are needed at all. When their mental condition improves and they are able to be about, it is best to give them light and easy tasks, which is better than attempts to improve the mental state by special exercise of an intellectual character. When one may be certain that they will receive good care at home and can be reasonably assured of their total abstinence, the patients may be allowed to return to their families.

In addition to the forms already described, there are other designations given to various mental states in which various symptoms predominate. Occasionally, in patients in whom excessive indulgence in alcohol, usually without food, has produced intense exhaustion with complete mental confusion, a state of *amentia* appears which simulates manic-depressive insanity. Following an attack of delirium tremens or acute hallucinosis, some sink directly into a paranoiac state or this less often develops primarily. The ideas of suspicion and jealousy greatly predominate and in many the delusions are predominantly sexual. They have the alcoholic emotional instability and may be dangerous. Since alcoholic excesses are at times a symptom of paresis, the diagnosis of this condition from the pseudoparesis of alcoholism may be difficult. The ideas of grandeur, the mental stupidity, with failure of memory and judgment of the paretic, are present with alcoholic hallucinations and ideas of persecution and infidelity; though the development is gradual and the course protracted, it is not progressive. Often the course is the final differentiation. If a chronic alcoholic survives long enough, the last stage of many of the above mental states is early senility and alcoholic dementia. This often occurs without any previous delusions or distinctly insane stages and is the final result of the cerebral arteriosclerosis and atrophy of the cerebral tissues.

Treatment of Chronic Alcoholism.—It is not always possible to obtain an accurate history of the length of a debauch or its intensity. If one studies the tremors in connection with the condition of the tongue, in the experience of the writer, a fairly good guess can be made. If the tongue is not coated and there is no tremor, the patient has been drinking about three or four days; if the tongue is moderately coated and there is no tremor, it means the debauch has lasted about five or six days; a heavily coated tongue and no tremor, about seven days; a moderately coated tongue and a slight tremor, about ten days; a heavily coated tongue and a marked tremor, about fourteen days; a moderately coated tongue with a very severe tremor, about three weeks; a fairly clean tongue and a severe tremor, about a month; a bright red, glazed tongue and a severe tremor, from six weeks to three months. This is true of young men up to about forty-five years of age; after that the tremor comes on earlier and a two weeks' spree will give as much tremor in an elderly man as a month's spree in a young man. In women these rules are not accurate; the nervous system is affected more intensely

and earlier, while gastritis comes on sooner. A week or ten days' spree brings usually an intense tremor and women will invariably endeavor to hide how much and how long they have been drinking.

The same treatment can be given to a chronic alcoholic as mentioned under delirium tremens. If a patient is furiously and fighting drunk, a hypodermic injection of apomorphine, gr. $\frac{1}{16}$ (0.064 gm.), will quickly transform the most pugnacious into a limp and docile object. He can then be put to bed and will drop off to sleep without further medication. This rarely causes vomiting unless the stomach is full. If it does occur it is of no disadvantage.

Often after a spree the patients feel a disgust for alcohol. But in many of the chronic alcoholics there remains always the nagging desire for it. The following treatment can be given as soon as the patients are manageable: We must clear them of the poison and then endeavor to solve the individual problem either mentally or socially that persistently drives a man to re-poison himself. The following treatment will do more to bring a patient to as near a normal condition as possible than any treatment that has as yet come to the writer's notice.

The same belladonna mixture is used as in morphinism (15 per cent. tincture of belladonna two parts and one part each of the fluidextract of hyoscyamus and the fluidextract of xanthoxylum). This mixture is given every hour of the day and night, beginning with six-drop doses and increasing two drops at the end of every six hours until the patients are taking 16 drops, or until dryness of the throat, dilatation of the pupils, or a belladonna rash shows that the patient has reached the limits of tolerance. Some patients can take but little of this mixture, one to two drops every hour, but as long as they obtain the full physiological effect as judged by belladonna symptoms they obtain the desired results. With the first six drops of this mixture from 2 to 5 compound cathartic pills and 5 grains of blue mass are also given. Five to six hours after this they are given a dose of saline. At about the eighteenth to the twentieth dose of the belladonna mixture they are again given 3 to 5 compound cathartic pills with 5 grains of blue mass, followed by a saline five hours later, and again at about the thirtieth dose of belladonna mixture the pills and the blue mass are again repeated and again at about the forty-second hour. Often when these last cathartics act, green bilious stools will appear and 1 to 2 ounces of castor oil should be given and the treatment stopped. Sometimes it is necessary to push the belladonna mixture higher than 16 drops to get the symptoms of full tolerance and to obtain the biliary reaction. Sometimes it is necessary to carry this belladonna treatment over the sixtieth or even into the seventieth hour with extra dosage of cathartics every twelve hours as above.

In young vigorous patients who have not been on very long sprees the alcohol can be withdrawn immediately. The general run of patients, however, are more easily treated by "tapering off," and in older or very nervous patients who have been on a prolonged debauch, it is necessary to give 2 ounces of whisky for four or five doses during the first twenty-four hours. These patients should also have cardiac stimulants such as strychnia and digitalis after the first twenty-four hours, sooner if they

are weak. To make these patients sleep the use of chloral hydrate and morphine as described under delirium tremens is recommended. If the patient has alcoholic gastritis and is nauseated or cannot retain his medicine, it is wise to give him 10 to 20 grains of sodium bicarbonate or sodium citrate every hour for five or six doses. In severe cases the addition of 5 grains (0.3 gm.) of Tully's powder (*pulvis morphinae compositus*) at four-hour intervals for two or three doses is beneficial. Often the sodium citrate can be given with 10 to 20 grains of cerium oxalate, if desired, some hours after the Tully's powder has been cut off. If, in the chronic alcoholic, delirium tremens appears during this treatment or following it, it may be necessary to stop the regular treatment and keep the patient asleep with hypnotics, giving him his cathartics once in twenty-four hours and giving abundant nourishment, as milk and eggs. Ordinarily milk does not agree with patients who are taking the belladonna mixture and a light diet of eggs, broths, and bread and butter or a small amount of meat and green vegetables can be given.

A treatment recommended by McBride, of Toronto, has proved very successful in his hands and has an advantage that patients need not be confined to an institution but can be at home or even at their daily work, coming to the office for treatment. The writer has tried it in a few patients with good results. As soon as the patient is over the severe effect of his debauch or if he is steadily drinking, he should be given hypodermically, three times a day, atropia and strychnia, of each gr. $\frac{1}{100}$ (0.00065 gm.). These drugs should be gradually increased until the full physiological effect of the atropine is obtained and the patient is taking $\frac{1}{30}$ or even $\frac{1}{20}$ of a grain of strychnia three times a day. When the mouth is continually dry and the pupils dilated the atropine should be reduced slightly and held at this dosage for four or five days. Then both the strychnia and atropine should be gradually reduced and finally the patient given the drug twice daily, then once a day, and then stop entirely. The time required is about one month or six weeks. Often the compound tincture of cinchona is added, especially in the morning, when the craving for alcohol is greatest. It is a noticeable fact that after a few days, usually in less than a week, the desire for alcohol has ceased and the thirst from the dryness of the mouth is easily satisfied with water. This has not been universally successful but has succeeded in a large number of patients.

These treatments are really but the beginning stages of what is necessary to help those addicted to excessive indulgence to a permanent regeneration. These drug treatments are the means by which we can eliminate the remains and the effects of the alcohol, can relieve the patient from his nervousness and intense physical craving for the narcotic. To many who have still a vigorous personality, who simply require the opportunity for physical relief from the poisoning which drives them to drink again, this is sufficient and they go on free from their addiction. But these are the exception. Most patients must be treated mentally and physically and be watched and cared for for a year or two before one feels sure that they will not relapse. The best method is to treat the patients physically and build them up thoroughly by as vigorous exercise as their

age and circulatory apparatus will permit. Most of these patients are intellectually twisted and their point of view distorted and often perverted; they are the misunderstood, the misplaced, the misfits of society. Sometimes this is only true in their own minds and they have misunderstood their environment. In many, unfortunately, it is really true. Psycho-analysis and mental therapeutics coincident with drug treatment will do more to help these patients than any other form of treatment. They should go to some institution where they can be properly cared for and be built up mentally as well as physically.

The poorer masses of society, those that crowd into the great hospitals and alcoholic wards, are unfortunately in no position to obtain this form of treatment. Public opinion has not yet awakened to a realization that these human beings are poisoned and in need of hospital and regenerative treatment rather than jail and punishment. A few States have realized in a measure these facts and through inebriate farm colonies are endeavoring to work out these problems. All social reforms are necessarily slow because to be successful there must be a rearrangement of the public point of view and a growth of new ideas in the average mind. But the regeneration of the mass of alcoholics in a community must be done through the care and control and regeneration of the individual and not through the condemnation and punishment of all individuals in a routine mass as is usually done.

OPIUM

Etiology.—The more highly cultivated and mentally developed a race becomes, the more intolerant is it of pain. This is especially true of the male sex. The Eastern nations have long used opium; thus in India and China opium, seems to be more often used in moderation without producing the same deleterious effects as in other races. In America the great majority of morphine habitués have drifted into the habit through the prescription of physicians or through self-medication. Formerly many became addicted to morphine through the widespread custom of giving it to relieve pain following operations, but the number has diminished since the danger has been recognized by surgeons. Today it is the prescription of the physician that is usually at fault. There is abundant testimony to show that 80 per cent. of them, outside of the dissolute and criminal classes, have acquired the habit through legitimate medication. A small number have drifted into its use through proprietary medicines. Many of these patients are neurotic from inheritance, are unstable, and are prone to stimulate to increase their mental vigor, or they are exceedingly intolerant of pain. They are often the children of alcoholic, tuberculous, syphilitic, or neurotic individuals, and, unfortunately, the alcohol in the parent need not be more than the so-called moderation. Recurrent headaches from faulty metabolism are a not uncommon cause of morphinism. Often strong and vigorous individuals after some shock, disappointment, or intense strain are given morphine to alleviate insomnia and soon become addicted to its use. Patients

suffering from painful affections or incurable diseases become addicted to morphine from the necessity of alleviating pain. Women suffering from disorders of the genital organs fall easy victims. Among the dissipated and vicious, morphine is indulged in as a luxury and to ease the recovery from their excesses.

Among Western nations the opium habit is indulged in more by the taking of morphine by mouth or hypodermically, or by drinking laudanum or paregoric, than by the smoking of opium. Among Eastern nations the smoking of opium seems rather to predominate. A few cases of codeine and heroin addiction have come under the writer's care, one patient taking 30 grains of codeine a day. The heroin addiction is more frequent than is usually realized. Compared with alcohol, opium may be said to be equally degrading and destructive of the moral side of the individual, but it does not leave behind it the same amount of organic lesions in the individual nor transform the individual into the same vicious, destructive, and abusive beast that alcohol does.

Acute Opium Poisoning.—Symptoms.—These require little detailed description; the infrequent, stertorous breathing, the livid cyanotic appearance, the small pupils, the cool, sweating skin, give a well-known and easily recognizable clinical picture. The respirations may simply be infrequent with a rhythmical regularity or they may be in groups of three or four with many seconds between each group.

Treatment.—This is chiefly a struggle to keep up the working of the paralyzed respiratory centre. The old method of walking a patient up and down, injecting large doses of atropine and slapping him with wet towels, has always seemed to the writer ill-advised. The incessant walking up and down, staggering forward and back, half-asleep, exhausts the patient thoroughly and the liability to give, what is for that patient, an overdose of atropine and thereby add its poisonous effects, appears to be a dangerous procedure. One may see patients, brought to the hospital with their hearts very rapid from an overdose of atropine, die suddenly in collapse; they really died from the antidote and not from the opium. The slapping with wet towels soaks them with cold water and in the exhausted condition there is a strong liability that pneumonia may follow. As soon as possible the stomach must be washed out with a solution of potassium permanganate (1 to 500); a certain amount of this should be left in the stomach; whether opium be taken by the mouth or as morphine, hypodermically, the morphine itself is excreted into the stomach cavity and is then reabsorbed. It has been proved experimentally on dogs that more than half of the morphine given subcutaneously can be recovered by simply washing out the stomach. Moor has shown that permanganate of potassium prevents the toxic action of morphine. In opium or morphine poisoning it is therefore wise to wash out the stomach at least every hour and leave a little of the permanganate solution in the stomach to destroy any of the alkaloid that may be excreted by the gastric mucosa. In the periods between washings a strong infusion of coffee should be injected into the bowel. Artificial respiration should be kept up until the patient is able, when let alone, to breathe eight to ten times a minute. This may mean many hours of

hard and tedious exertion, but as long as the heart is beating, if respirations are kept up, there is a possibility of recovery. To relieve the cerebral venous congestion produced by opium, the injection of ergot, hypodermically, as described under alcoholism, is most effective and satisfactory. It equalizes the circulation and relieves the congestion.

Opium Smoking.—The smoking of opium is an ancient addiction and compared with the other uses of opium takes longer to form a real habit, works less physical and mental injury, and is easier to cure. A gradual rise in the amount used is necessary in order to get the desired effect; the early pleasurable symptoms soon disappear and the evil effects on mind and body are similar in many respects and the symptoms incident to abstinence are the same. In smoking opium, the morphine is not all consumed and a large amount remains in the ash. Kane gives the tabulated statement of the daily dose of 1000 Chinese smokers: 646 varied between 16 and 128 grains; 250 from 160 to 320 grains; 104 from 480 to 1600 grains. To obtain the desired effect 5 grains seem sufficient for a novice, while old smokers need as high as 290 grains. The average American seems to consume more than the average Chinaman to obtain the desired effect. This vice among Americans is of relatively recent origin, having been first taken up in this country in 1868, in San Francisco; from that time it rapidly spread through the West and from there to the East, until now throughout the United States it is by no means rare.

Symptoms.—The effect of opium smoking on a novice is described by Kane: the first effect was nausea and dizziness, accompanied by a pleasant sensation of exhilaration, followed by a quiet, easy contentment; this was after deeply inhaling four pipes; there was an increase in the force and frequency of the pulse from 80 to 110, hot flashes over the body and face, and after a few more pipes came a soft pulse, lessened in frequency, and a fall in temperature, giddiness, and slight nausea, with some staggering on rising or walking, profuse perspiration, ringing in the ears, and intense itching over the entire body. The profuse perspiration and nausea continued, followed shortly by abundant and easy vomiting; there was also a feeling of uncertainty in putting down the feet in walking, sleepiness, heaviness of the eyelids, contraction of the pupils, dryness of the throat, and a fear of crossing the street if a wagon or car was approaching. The sexual appetite was increased. This was followed by intense sleepiness. The doze, however, lasted but a moment, the awakening being sudden; there were no dreams. The nausea was a prominent and distressing symptom and, in his case, lasted for twenty-four hours as did also the itching. Sometimes the novice does not feel at all sleepy and becomes very talkative even after the tenth pipe, and later, when desiring to sleep, although sleepy, he is unable to do so from intense fear that some catastrophe may occur. Among other novices the drowsiness comes on after four or five pipes, and they sink back into a heavy slumber, lasting for some hours. Twenty-four hours after smoking, the novice frequently feels languid, is without appetite, has an intense headache, and the itching continues. Old smokers do not, as is usually believed, smoke a few pipefuls and then fall into a heavy sleep; as experience grows into a habit, stupefaction is less speedy, and it may require many

hours and many pipes before even the coveted excitation is reached, and the majority complain that they are sleeping less than usual and are troubled by distressing insomnia.

The effect of opium smoking is first seen upon the mind. The feelings of pleasant exhilaration and contented indifference are gradually more difficult to obtain and, after from three months to a year, they cease to occur, although the amount of opium smoked be largely increased. The continuance of the smoking brings with it a disinclination for continued mental effort, a weakness of the will-power, a lack of decision, and a loss of memory. A certain indecision, manifested by mental perplexity and impatience concerning the smallest actions, is often noticed after smoking. During periods of despondency, suicide, especially in women, is not uncommon. Neuralgias, noticed in other forms of opium taking, are rare during opium smoking. Occasionally colic is complained of, but this seems more due to intestinal disturbances than to a direct effect on the nervous system. Tremor of isolated muscles sometimes occurs, but a general tremor, most marked in the hands and tongue, is noticed when smoking is excessive. The pupils, as a rule, are evenly contracted. When the effect of the last dose has worn off, the pupils are often widely dilated, and conjunctivitis, with burning and excessive lachrimation, is common. The pulse-rate is usually above normal, except that after excessive smoking it falls below the normal rate. The flushing of the face with profuse perspiration in a novice is replaced, in the old smoker, by a sallow and deathly hue. When under the full effect of the opium, the respiratory rate is lower and prolonged smoking produces a chronic bronchitis with cough, and pharyngeal and laryngeal catarrh with loss of power in the vocal cords. In the alimentary tract there is gastritis and constipation, often accompanied by hemorrhoids and an obstinate pruritus. The constipation is at times succeeded by a violent diarrhœa, which may become chronic and last for months.

The itching of the skin varies with the individual; in some it is slight and in others intense, especially in the genital region, so that they often excoriate themselves. For the first few months of smoking, in both sexes there is an increased sexual desire which is especially marked in young women, and opium smoking has been used as a means of seduction. After a few months there is a diminution of desire and impotence in the male. In the majority of women menstruation is not interfered with, although in some it is scanty and irregular, and there may be amenorrhœa. In this, opium smoking differs materially from morphine addiction. Some women who smoke excessively habitually miscarry; in others it seems to have no effect whatever upon their pregnancy, and the children of some opium smokers, so far as can be learned, seem strong and healthy.

The symptoms of abstinence and the sudden cessation of opium smoking are the same in most respects as follow the withdrawal of other forms of opium, but the smoker often suffers less severely and for a shorter time. The respiratory tract and the eyes are affected out of proportion to the rest of the body. The first symptoms are gaping, yawning, sneezing, profuse discharge of tears and mucus from the eyes and nose, irregu-

larity of the pupils, ringing in the ears, followed by extreme restlessness, intense pain in the joints, nausea, vomiting, and purging. A peculiar dull, drawing, dry, and burning ache in the pharynx and larynx occurs, which is followed by distressing pains in the muscles, especially in the calves of the legs and between the shoulders. Chills, followed by flashes of heat, are felt along the spine and are followed by profuse perspiration. In some cases, if no opiate is used, the vomiting and diarrhœa continue and the restlessness and flushed face give place to complete relaxation, a gastly pallor with sunken eye, collapse, and death; but in less severe cases or when proper remedies are used, the distressing or dangerous symptoms cease one by one. Sleeplessness persists for a long time; the bronchitis and catarrhal inflammations of the throat usually last for months; the pains in the legs and body gradually disappear; the sexual power returns; the appetite gradually improves and becomes ravenous; an increase in the weight is manifested; a return to natural buoyancy of mind begins, and the patient regains his health and strength. When once cured, it is difficult to say what proportion relapse, but a single indulgence may be sufficient to start them again into the habit. Rarely, individuals are found, who having broken the habit, return to it and smoke but one pipe a week and do so for years without apparent injury.

Opium by Mouth.—This is much more widespread in this country than is generally realized. Probably the most of the opium takers are those suffering from "rheumatism," neuralgias, migraine, hepatic or renal colic, dysmenorrhœa or other troubles which at first caused only a temporary indulgence. Opium is often used at intervals for insomnia or to allay grief and mental suffering. It is given up when the strain is past, and taken up again for any reason that seems sufficient. Often in these cases the only symptoms seem to be a mental and physical restlessness and anorexia, with a disposition to sleep. The opium taker shows certain differences from the individual taking morphine. There is more excitement and exaltation following morphine, while with opium there is more a feeling of quiet contentment, lasting over a long time. The morphinist, after the feeling of satisfaction has worn off, is more apt to dread the slavery of his habit, while the opium taker never seems fully conscious of the danger. The opium taker rarely consumes as much as the morphinist and the duration of his existence, after the habit is once formed is usually much longer. He may indulge for a year or more without apparent injury, but the morphinist in a relatively short time, shows evidences of his degeneration and succumbs quicker.

Gradually the effects of the opium begin to show when used to excess. There is a change in the disposition; the individual becomes irritable, peevish, somnolent, and shows evident dishonesty in little matters, especially concerning the use or the procuring of the drug. A sallow parchment-like complexion is common, although in the early stages the face may be flushed, with a tendency to cutaneous eruption; the hair tends to become gray early and there is an old, exhausted, or cachectic appearance. There is often general feebleness with tremors, and this may be so pronounced as to resemble ataxia. Sometimes the imagination seems stimulated for a while, producing a dreamy, visionary state, but it is

extremely doubtful if, under the influence of opium, the mind is capable of more intellectual vigor. There is a tendency to ignore and to break appointments and social engagements. If the opium taker is found in company, it is usually among those who are below him in intellectual and moral development. His self-respect is gone, he is careless of his appearance, indolent in his habits, and neglectful of the decencies of life. In the later stages cardiac degeneration is prone to occur with attacks of pseudo-angina pectoris or with precordial anxiety; constipation is common, and the general nutrition is much disturbed.

MORPHINISM

Indulgence in morphine is a development of recent years; it has taken the place, especially in large cities, of the preparations of crude opium. The readiness and cheapness with which morphine can be obtained and the ease with which hypodermic syringes can be bought have made this addiction a widespread curse. Physicians, nurses, and pharmacists form, unfortunately, a large percentage of the habitués. Some take it only to assuage pain, and only use it when the pain becomes almost unbearable. The dosage in these patients is increased only as the need demands, and often the same dose will suffice for many months or years. In the end, many of these show the symptoms of chronic morphinism, but French writers differentiate this class of patients from those who take morphine for pleasure, in whom the habit rapidly grows. These authors designate the first class as morphinists and the second class as morphinomaniacs. The question may arise in the case of a patient suffering from a painful and incurable disease, whether a physician is justified in giving morphine, knowing that if once used it must be given for the remainder of the patient's life. True it is that morphine given daily for two or three weeks, even in small doses, is sufficient to cause a habit, although many patients resist longer than this. The habit is always formed through the repeated administration of small doses, and the idea that because the dose is small no habit will follow has led to many addictions. Although people are often opposed to having it said that members of their family died with the morphine habit, yet in many cases of incurable disease it is simply cruelty to refuse to give it and the formation of a habit in some sufferers is of no consequence.

The hypodermic use of morphine is the most seductive form of the habit and the hardest to break; some patients seem to require the sensation of the needle thrust in order to be satisfied. In many who take enormous doses it would seem that all the morphine does not act, but some must remain inert and be excreted without action. Mithridatism, or the inability to be killed by opium and morphine, seems to occur in those taking over 30 grains a day. The writer has seen one patient take in a single dose 45 grains of morphine hypodermically and only become comfortably drowsy, and another patient take 47 grains within two hours and show no effect except satisfied contentment.

Considering the symptoms, memory is one of the faculties first affected

and the amnesia is similar to the beginning senile dementia. Names are the first to go; the morphinist will relate occurrences early in his life, but will forget what he has done during the past week. He will forget the familiar names of streets, the details of his profession; thus the physician forgets the dosage of medicines and the scientific terms with which he is familiar. Amnesia of the well-marked stage of morphine intoxication is only equalled by the amnesia of paresis. The will power is enfeebled and the patients spend days in bed without sleeping and without stupor; their minds are perfectly clear but their power to do is gone. In some patients this is continuous and permanent; in others it seems to run in crises, lasting over two or three days. There is psychic asthenia. The sense of responsibility is wiped out and is replaced by the indifference of perfect egotism. Their character is modified and they are discontented grumblers, obstinately "ugly," often given to explosions of intense rage, quarrelling without cause, and even destructive and dangerous to those with whom they come in contact. Often the morphinists are individuals of more than average ability and intelligence, realizing fully their condition, and appreciating their progressive degeneration. It is for this reason that they resent criticism and accept reproaches about their habit with bad grace, because they are already filled with remorse. Morphinists usually lie about their addiction because in the early stages they feel that others consider it a vice and a disgrace, however innocently it may have been acquired, and they have enough moral sense left to endeavor to hide it. If, however, they have just taken their morphine or are assured of sufficient dosage to keep them comfortable, they do not necessarily lie about other matters. The fear of being deprived of their drug is an ever-present horror. Patients have come under the writer's notice who were literally starving to death and yet they had means kept to procure the necessary amount of morphine to prevent them going through the horrors of forced withdrawal without assistance. When the craving for the drug is upon them, there is nothing to which they will not stoop to obtain it. Lying, thieving, begging in the street, prostitution itself, are to them all justifiable means to obtain the drug.

Morphinists do not sleep well; they are subject to nocturnal hallucinations which render their nights times of terror; thus they endeavor to keep themselves awake by reading, and during the daytime are prone to fall asleep whenever they remain quiet, sitting in a chair, no matter in what place or company. The hallucinations of sight are always terrifying, and contrary to the hallucinations of alcoholism, those of morphinism are not occupation deliriums. The hallucinations of sight are the most frequent; next those of hearing; those of taste and smell are rare, and those of general sensibility are exceptional, which last is also contrary to what occurs in alcoholism. The sense of taste is often dulled and sometimes even abolished. Reading and writing become impossible because objects appear clouded and deformed, and when the endeavor is made to fix an object, it dances or trembles or approaches or retrogrades, and this, together with a frequent distinct photophobia, causes great distress. Ophthalmoscopic examination does not reveal

any distinct lesion. There is at times contraction, and at times dilatation, of the pupils; an anemia of the retina has been described. The visual disturbances disappear when the morphine is permanently withdrawn. The reflexes are very variable. Disturbances of the general sensibility are often marked and vary greatly; there are often paresthesias and sometimes intense neuralgic pains. Others show marked anesthesia, which may be confined to one side of the body. More often there is hyperesthesia, and the sole of the foot becomes so painful, that, when it is touched to the floor, it gives a sensation of burning, and the patient can only walk with short, jumping steps. Rodet considers this form of hyperesthesia as very characteristic of chronic morphinism. The tactile sensibility is usually diminished or abolished. The question often arises whether indulgence in morphine impels the individual to suicide. At times when, inadvertently, too large a dose is taken, the patient succumbs, but as long as he can obtain his drug, he is an individual without will, apathetic, and incapable of making sufficient exertion to commit suicide; if, however, the morphia be withdrawn or he cannot obtain it, the condition entirely changes.

Troubles of digestion are common; in the early stages there is nausea, vomiting, and anorexia, which do not persist for a very long time. There is often an intense thirst; the breath is very offensive and of a peculiar odor, often spoken of as being so characteristic as to designate the morphinist by those who are brought in contact with many of these patients. They are markedly constipated and this often alternates with attacks of diarrhœa; their stools are bloody and, during the period of constipation, may be as infrequent as once or twice a month. The teeth are subject to caries, which attacks first the molars on their grinding surfaces; this extends to the bicuspid, then to the incisors, and last of all to the canines. This is always painless, not accompanied by any periostitis, and usually progresses with great rapidity. It usually coincides with the falling out of the hair. The disturbances of nutrition appear in some patients after a few months and in others not until after some years. Emaciation is perhaps the most striking and may go on to an extreme degree. Their faces become livid and often sallow, the expression set, and there are premature wrinkles, which, with the faded, sallow look of the skin, often gives the look of premature old age. The tissues lose their vitality, which accounts in a measure for the ease with which slight bruises cause ecchymosis, and the greater liability to the occurrence of abscesses.

The pulse of the chronic morphinist is slow and there is a fall in arterial tension with, in the last stages, distinct enfeeblement of the heart's action and diminution in the force. The number of respirations is slowed and, at times, they are shorter, so that every now and then a long deep inspiration seems necessary to give the required amount of air. Dyspnœa on exertion, even of the slightest kind, is quite common. In the beginning of morphine addiction there is polyuria, which later is followed by a diminution of secretion below the normal. In many there is albuminuria which is ascribed by Levinstein to a special action of morphine on the medulla, to changes in the arterial pressure, or to a paralysis of the nerves

which enter the kidney around the renal artery. The effects in the genito-urinary system are much the same as those described under opium.

Most women become sterile, but in spite of the cessation of menstruation, conception may take place. Pregnancy may run its normal course, or the morphine may cause a miscarriage or premature birth. Children born of morphinist mothers may be well-formed and normally healthy. Often the children of morphinist parents are idiotic or show a lack of mental and physical development.

The accidents which may follow the injection of morphine are those of infection from the use of a dirty needle or of an infected solution. These abscesses usually appear at the point of injection, but sometimes at distant points, in a portion of the skin which has not been perforated. They are usually small, rather indolent, and not always as painful as one would expect. They usually heal under proper treatment, although they may form indolent ulcers. The points of injection may be the starting point of erysipelas, cellulitis, or phlegmon. Kane reports cases of tetanus developing from the hypodermic injection of morphine. Where the morphine has been injected directly into a vein, sometimes a sudden, intense narcotism follows and the patient feels a peculiar tingling over the entire body. There is at times a feeling of great fulness and throbbing in the head, and this may be accompanied by difficulty of respiration, swelling of the face, and loss of consciousness. Death has been reported as following quickly when morphine is suddenly injected into the circulation. Most habitués increase the dose so gradually that the accident of acute poisoning and death from an overdose is comparatively rare. When, however, an endeavor has been made to reduce the amount taken and then for some reason a larger dose is desired, an amount, which formerly could be borne with impunity, is taken and death results.

When once a person is thoroughly under the influence of the habit, a cessation of the use of the drug produces symptoms, both physical and mental, of such intensity that few are strong enough to resist the craving thus produced and, unaided, break off the habit. When the effects of the last injection begin to wear off, restlessness, malaise, yawning, and sneezing appear; the craving increases and can only be entirely relieved by a further dose. The length of time, after the last dose, at which these symptoms will begin, depends on the individual. Following quickly on the malaise, the eyes begin to water and the eyelids droop. The eyes lose their lustre and vision is much disturbed. The face becomes pale and an expression of intense distress is very noticeable. There is a trembling of the hands and of the arm, varying markedly from the alcoholic tremor. In this condition there is nothing that morphinists will not do to obtain the drug. As enforced abstinence continues, the patient may develop epileptiform attacks or hysteria, or there may be in neurotic individuals a state of choreic jactitation. In extreme cases a form of mania may develop in which the patient endeavors to commit suicide or attacks the attendants. Hallucinations of sight and hearing may develop, and these are always of a terrifying nature. This is most frequently seen in those who have taken cocaine or alcohol with their morphine, but not infrequently in those who have taken morphine alone.

Often, before these mental disturbances are fully developed, the patients are overcome with a sensation of extreme weakness and forced to keep in bed. They are pale and haggard; there is nausea and vomiting, and almost invariably diarrhœa, which may be profuse. This is often accompanied by intense abdominal pain and hyperesthesia of the skin, so that the patient can scarcely support the weight of the bedclothes; the body is often covered with a cold sweat, and there may be chills of great intensity.

When morphine is cut off abruptly there is great danger of collapse. This may supervene on the second or third day, and the patient shows increased weakness, appears pinched and haggard, while the pulse becomes small and then disappears. Or he may show a sudden high pulse tension, feebleness of the heart action, and suddenly, while wandering about restlessly, fall pulseless to the floor. Sometimes the fatal collapse may occur without warning while the patient is quiet. Still another form of collapse may occur; the face becomes deep red, the eyes shine brilliantly, the pulse falls to forty and the patient loses consciousness after a feeling of intense agony. These collapses may last for fifteen or twenty minutes; they may recur three or four times in the twenty-four hours, and the patient may recover or die in any of them unless morphine be given. Fortunately these attacks are rare when the drug is withdrawn gradually but they are fairly common when this is done abruptly. There are some few cases on record in which the fatal collapse occurred some time after the patient was convalescent and apparently well on the road to recovery. During their periods of suffering, the patients are apt to be afflicted with distressing insomnia, and, if they sleep, it is only in fitful dozes. In a longer or shorter time the suffering gradually subsides and the patient can rest with some degree of comfort; the morbid craving has gone; the appetite returns and often becomes excessive; in women menstruation is reëstablished, at first painfully, later normally. In both sexes the sexual desire returns, often painfully and excessively and then subsides. The patient goes into a rapid convalescence. When morphine is broken off, if it has been taken to quiet some neuralgia or to benumb some unbearable sensation, these pains, although quiescent during the period of the addiction, may return in full force when the habit is broken.

Treatment.—Most patients addicted to morphine have long ceased to obtain any pleasure from its use. They long to be free from its slavery and dread only the terrible suffering which the deprivation from the drug brings. The question arises whether they should be treated by the slow withdrawal method, in which they are treated symptomatically for whatever symptom seems most distressing, or whether the drug should be withdrawn abruptly and the patients suffer with full intensity, hoping to relieve them in a shorter space of time, or whether some of the more recent methods, using belladonna or hyoscine, should be employed.

The sudden withdrawal method does not seem justifiable. The danger of sudden collapse and death is not a theoretical one. Morphinism or the opium habit is a chronic poisoning and must be treated as such.

The only safe method is by the rapid elimination of the drug in the body, the quieting of the withdrawal symptoms with some preparation of the belladonna group, and as rapid a withdrawal of the drug as the condition of the patient will justify. Under these conditions collapse need not be feared, and the elimination of the poison and the restitution to health is soonest accomplished.

Lott, of Texas, was the first to use hyoscyne in the treatment of morphinism, giving gr. $\frac{1}{60}$ of the hydrobromide hypodermically every two hours for two or more days during which the morphine was withdrawn. The patient does not sleep but lies stupefied, mumbling continuously and picking in a restless delirium. Another method of combining hyoscyne with atropine and strychnine has been recommended by Wagner. This should not be pushed further than the mild delirium, for if hyoscyne is pushed too vigorously the patients go into an almost unmanageable delirium which can only be controlled by morphine.

Another treatment is known as the Towns method. This has the advantage that the belladonna and hyoscyamus do not bring the patients to a stage of delirium nor to the condition of helpless unconsciousness as hyoscyne does. These drugs are never pushed beyond the stage of dry throat and dilated pupils; the patients retain their consciousness and freedom of action. The mixture consists of two parts of a 15 per cent. tincture of belladonna and one part each of fluidextract of hyoscyamus and xanthoxylum. It seems necessary to push this mixture to tolerance of the belladonna. This varies with the individual, and some of the best results have been obtained with patients who could not tolerate more than two drops of this mixture as an hourly dose, while in others it was necessary to push the mixture up to eighteen or twenty drops or even more. The bottle containing the mixture must be kept well corked and shaken before using. The details of the method are as follows:

The patient is given 5 compound cathartic pills and 5 grains of blue mass, and six hours later, if these have not acted, they are followed by a saline; after three or four abundant movements of the bowels the patient is given, in three divided doses at half-hour intervals, two-thirds or three-fourths of the total daily twenty-four-hour dose of morphine or opium to which he has been accustomed. The larger amount of the drug is an advantage as the patient is less likely to feel discomfort just before his next dose. Observe carefully, however, after the second dose has been given, as the amount then equals four-ninths or one-half the total twenty-four-hour dose. Some patients cannot comfortably take more than this amount. With morphine, the 6 drops of the belladonna mixture are given in capsule. This belladonna mixture in doses of 6 drops (drops dropped from an ordinary medicine dropper—not minims) is given every hour for six hours. At the end of six hours the dosage is increased 2 drops. The belladonna mixture is continued every hour day and night continuously throughout the treatment, increasing 2 drops every six hours until 16 drops are taken, when it is continued at this dosage; it is diminished or discontinued at any time if the patient shows belladonna symptoms, such as dilated pupils, dry throat, or redness of the skin, or the peculiar incisive and insistent voice, and insistence on one

or two ideas. It is begun again at reduced dosage after the above symptoms have subsided.

At the tenth hour after the initial dose of morphine is given, the patient is again given 5 compound cathartic pills and 5 grains of blue mass. These should act in six or eight hours, but if not a vigorous saline is given; when they have acted thoroughly, the second dose of morphine is given, which is usually about the eighteenth hour. This should be one-half the original dose, *i. e.*, one-third or three-eighths of the original twenty-four-hour daily dose. The belladonna mixture is still continued, and ten hours after the second dose of morphine, that is about the twenty-eighth hour, 5 compound cathartic pills are again given and 5 grains of blue mass; these if necessary followed by a saline six or seven hours later. After these have thoroughly acted at about the thirty-sixth hour, the third dose of morphine is given, which is one-sixth or three-sixteenths of the original dose. This is usually the last dose of morphine that is necessary. Again, ten hours after this third dose of morphine, *i. e.*, the forty-sixth hour, 5 compound cathartic pills and 5 grains of blue mass are again given, followed seven or eight hours afterward by a saline, and one expects at this time to see a green stool appear. When this appears, after the bowels have moved thoroughly, about eighteen hours after the third dose of morphine, 2 ounces of castor oil are given. If at any time a patient is nauseated, calomel in small doses with a little soda can be given at half-hour intervals instead of the cathartic pills. Often it is necessary to continue the belladonna mixture for one or two further cathartic periods before the bilious stool will appear, codeine being used to ease discomfort. During this last period when the bowels are moving and before the oil is given, the patients have the most uncomfortable time. The nervousness and discomfort can be controlled usually by codeine, which can be given hypodermically in 5 grain doses and repeated if necessary, or dionin or some form of the valerianates may help them. About the thirtieth hour these patients should be given strychnine or digitalis, or both. After they are free of morphine, the tonics which do the most good are those which contain some form of phosphorus and arsenic.

There is a danger to these patients in overeating, and thus bringing back withdrawal symptoms due to disturbance of digestion. They have been in the habit of referring all uncomfortable feelings to the withdrawal of morphine, and digestive disturbances feign these symptoms. Sometimes about the thirty-sixth hour the stools become clay-colored. Some form of prepared oxgall in small doses every hour for five or six doses is most effective to stimulate further biliary secretion.

The question arises whether the treatment should be undertaken in the patient's home or in some institution. There is no question, if patients will go to an institution, that they will go through with less pain and suffering, for they will be cared for by physicians who are dealing with this treatment and alleviating the symptoms which vary in each individual patient; and a morphine patient requires constant attention.

The pains in the legs and knees are often relieved by a combination of phenacetin, aspirin, and caffeine, by antipyrin or pyramidon, or doses

of sodium salicylate. Sometimes it is wise to carry on the morphine through the fourth period, not cutting it off after the third, especially in those who are taking large doses and who are physically much below par. When giving codeine for the relief of nervousness and distress, it is safe to calculate that 1 grain of codeine is equal to $\frac{1}{8}$ grain of morphine, and $\frac{1}{2}$ grain of dionin is equal to about 1 grain of codeine. Heroin is stronger than morphine; about $\frac{1}{12}$ of a grain of heroin is equal to about $\frac{1}{4}$ grain of morphine. Heroin, is dangerous to give in tiding over the distress, simply because it is adding to the narcotic, and codeine and dionin are preferable. But if a patient is given codeine or dionin longer than forty-eight hours after morphine is stopped he will acquire the necessity for codeine or dionin. Therefore these other salts of opium should be used only to ease discomforts during the last stages of the treatment and later if he still feels discomfort in too great a degree. Patients sometimes show an idiosyncrasy against codeine and it produces a burning and redness of the skin or sometimes an urticarial rash with intense heat and itching. This quickly passes, but dionin will have to be substituted.

The after treatment is of great importance. The patient should be built up physically. Men should be sent to some physical trainer where they are built up into good physical condition. If this is not done they drift into an irritable, discouraged, neurasthenic condition in which they are very prone to go back to their narcotic. If, however, they are properly built up, at the end of a month they will have gained flesh, their anemia will have disappeared, and they will be in excellent health and spirits. Morphine or opium in any form must be strictly guarded against. This treatment in my hands in some 800 patients has proved so successful that 80 per cent. have remained well. This proves the efficacy of this method of treatment and also that most morphinists, if free from their addiction, are anxious to remain clear.

COCAINE

The pure cocaine habitué is not as common as the morphinist or the alcoholic. The drug is usually taken to overcome the nervousness of an alcoholic debauch or the depression following morphine. It is not infrequently used to relieve the exhaustion following sexual and alcoholic excesses. Judging from the statistics of drug-store sales, cocaine habitués seem to be most common among the very poor and among the wealthy. Cocaine is contained in certain quack nostrums. In the Southern States, cocaine addiction is very common among the negroes. Snuffing the powder or a solution of cocaine is a common method of use. It is often taken hypodermically, and, when thus used in impure form, it sometimes causes a green discoloration, which remains permanent at the site of the injection in the skin. Patients suffering from neuralgia, local or general, physicians exhausted and anemic, who have to be tided over some strain, neurotic and psychopathic individuals, the wornout and failures of modern life, fall easy victims.

Acute cocaine poisoning is seen following the injection of the drug to obtain its local effect in surgery. Death is reported as having occurred in forty seconds following 12 drops of a 4 per cent. solution given hypodermically to a girl of eleven years. Half a grain to one unaccustomed to its use seems often to be a borderline dose. Such small doses as 4 drops of a 2 per cent. solution in the eye, produced in an old woman an intoxication which lasted for four days, and even 1 drop of a 1 per cent. solution in the eye of a child fourteen years old has been followed by symptoms of active poisoning. There is a strong idiosyncrasy, and while such small doses have caused death, recovery has followed such large doses as 22 grains by the mouth and 10 grains hypodermically. In the mild cases of poisoning the ordinary symptoms are great restlessness and nervous excitement, with no feelings of pleasure or comfort, but rather those of anxiety and even terror, an increase in the frequency of the respirations, and often a distinctly accelerated pulse-rate, with the patient pale, faint, and dizzy. In the more severe poisoning there has been nausea and vomiting, a rapid and imperceptible pulse, great nervousness and jactitation; the patient feels as if the heart would stop beating; intense perspiration and collapse with or without loss of consciousness are seen; the pupils are usually dilated; in some they have been reported as contracted, and, occasionally, the pulse has been slow and feeble with slow and infrequent respiration, or Cheyne-Stokes breathing with marked cyanosis. After large doses, convulsions are frequent and often of a violent epileptiform character. At times these are partial, with unilateral or bilateral cramps in the muscles, chiefly in the flexors; these muscular spasms may go on to general rigidity and opisthotonos may be produced. Consciousness is usually lost but sometimes there is mania with hallucinations and delusions which have frequently been violent and even homicidal. The treatment of the poisoning is symptomatic: the patient should be kept in a horizontal position and given aromatic spirit of ammonia, alcohol, camphor, or caffeine. If the poisonous effects are manifested in the respiration, oxygen or even artificial respiration should be used. Intravenous injections of normal saline solution have proved helpful. If the drug has been taken by the mouth, the stomach should be washed out. After the patients have recovered from this acute poisoning, nervous disturbances, such as insomnia, vertigo, tingling in the limbs, and mental depression, may continue for some days.

Chronic poisoning by cocaine is both periodic and continuous. The periodic form is characterized by the excessive use of the drug for several days or weeks, after which it is abandoned and there is a period during which there is no desire for it. During the free intervals the patient remembers distinctly the pleasurable mental impression which he obtained, declares that he has broken from its use and that he will not use it again, but as soon as the cause returns which formerly drove him to the use of the drug, he will invariably reason that there is no danger in using it for a short time, and resumes its use. Soon the free periods become shorter, and those of addiction longer, and its use becomes continuous. These persons also show the peculiarity that in order to

conceal the habit they take other drugs, such as alcohol, chloral, and morphine, and when they cannot obtain cocaine they turn to any drug that will quiet the nervous system. Some become violently maniacal, and when given the drug almost instantly quiet down.

The main pleasurable action is the feeling of exhilaration and increased mental and muscular strength and with this there soon develop delusions of great strength and vigor, the patient feeling as if he had absolute self-possession; he shows great activity, talks freely, and enjoys everything; each sense seems to be gently heightened. Finally hallucinations of voices begin to appear; there are delusions of persecution and fears of personal injury; insomnia comes on with great muscular restlessness and agitation, which simulates the irregular spasmodic movements of chorea major. They show a profuse volubility, talking in a wide discursive manner over all subjects and in their writing or speech there are no pauses, no dividing lines, no purposeful connection but a steady, connected flow of words, involved and without point, without direction, and without end. The patient will endeavor to convey some idea or belief, and after the first few sentences the purpose is forgotten and he wanders on in great prolixity and diffuseness. Thus many cocainists are great letter-writers, and in some instances the letters have taken on an amatory type. This same prolix type, in other instances, has taken on a slanderous form, but there is a noticeable lack of bitter, sharp accusations and distinct charges; the meaning of the letters can only be made out by inference from the involved mass of words. Again, hallucinations of sight and hearing develop, and the patients see suspicious characters watching them and hear voices plotting to do them injury; they begin to take unusual precautions and are prone to carry revolvers and knives to defend themselves.

In the early stages of cocainism, when the effect of the drug begins to wear off, the patients become morose, irritable, easily excited, and suspicious; there is insomnia and an impending sense of trouble and danger. In the later stages, the exaltation periods are brief and are followed by stupor and restlessness with evidences of great mental disturbance. The appetite fails; they are anemic, and emaciate very rapidly; look sleepy and tired; the skin becomes flaccid and pale; the senses of sight, hearing, and smell are seriously impaired, and there is a feeling of paresthesia in the skin, giving a sensation as if vermin were crawling on it, which is a very significant symptom. Although there is increased sexual excitement, the sexual power is diminished. Kraepelin describes a definite psychosis which may develop on the basis of chronic cocainism and which bears a close resemblance to alcoholic delusional insanity. It begins with a few days of irritability, anxiety, and restlessness, after which the hallucinations suddenly appear. Threatening voices are heard compelling the patients to act strangely; moving pictures are seen on the wall. Minute black specks, moving on a light surface, are very characteristic hallucinations, and may be mistaken for flies, mosquitoes, and other small objects. Paresthesias of the skin create the belief that they are under the influence of electricity or are being punctured with needles. Most characteristic is the sensation of foreign

bodies under the skin, particularly of the ends of the fingers and palms of the hands. Auditory hallucinations make them suspicious of their surroundings. They believe their thoughts are secretly being read or they are being spied upon through holes in the ceiling. The patients may try to kill their alleged tormentors or attempt suicide. They have characteristic delusions of infidelity which come on as an acute symptom. These are often obscene in character and they will accuse their wives of the grossest immorality. They are prone to react to these false ideas in a vindictive and aggressive manner. Consciousness remains clear and orientation is good except in rare instances when the excitement is very great or after the fresh injection of the drug. The emotional attitude is dejected, excitable, irritable, and even passionate; more rarely they are reserved and reticent concerning their delusions. Their actions are usually restless and unstable, though some may appear orderly.

Cocaine delusional insanity develops rapidly and may run its full course in a few weeks. The symptoms increase under the influence of a single dose. The delirious state soon disappears if the drug be completely withdrawn, but the delusions may remain for weeks or months. Morphinism and cocainism in the same individual often lead to a combination of symptoms, but morphinism, except with cocainism, seldom produces a rapid development of pronounced mental disturbance. The cocaine psychosis develops more rapidly, the symptoms are more severe than in the alcoholic delusional insanity, and the delusions of jealousy appear earlier and are an acute symptom. A single dose of cocaine produces an exacerbation of the symptoms, while in alcoholism it produces little or no effect. The sensation of objects under the skin is characteristic only of cocainism.

Diagnosis.—This is often very difficult. In some patients there is only an increased buoyancy of spirits and an increased desire for mental and physical exertion, but if their work is studied closely, its character and the judgment displayed in doing it are below the former excellence. These patients show defects of judgment and a diminished sense of ethical duties; they are also more prone to be reckless and aimless in their thoughts and work, and show a diminution of ambition and will power. The powers of connected application are less, and often a noticeable symptom is periods of buoyancy varying with periods of beginning depression, and a disposition on the part of the patient to go off alone; and on his return the old buoyancy and confidence have returned. Thus the cocainist differs from the alcoholic by his periods of secretive solitude and from the morphinist, in the later stages, by his delusions of persecution. When cocaine is the main drug and alcohol and morphine are taken to relieve it, the periods of exaltation and delusions of persecution are very noticeable. If cocaine is taken to relieve morphine or alcohol, the peculiar symptoms of cocaine are usually absent and there is simply a restlessness and insomnia. Morphine and alcohol, taken after cocaine, intensify the injury to the nervous system and both mania and dementia are apt to follow.

Prognosis.—In the early stages, when cocaine is taken alone, if the proper treatment can be instituted, the habit seems to be more easily

broken than that of morphine or alcohol and the chances of a permanent cure are greater. If, however, the habit is well-established, complete recovery is obtained with greater difficulty.

Treatment.—In treating cocaineism we must realize that there is no drug which brings with it such a blissful sense of satisfaction and of relief from mental or physical pain, or gives such a sense of increased vigor and the ability to do all that the mind craves or hopes for. The effect is very intense, and, although the patient may realize the danger of relapsing, the mental impression made under the influence of the drug is so strong that the tendency to relapse is very great. The most effective treatment is the Towns treatment and the method is the same as in dealing with an alcoholic, except that the cocaine should be cut off immediately. Strychnine, with or without some form of digitalis or sparteine, should be given from the beginning. The belladonna mixture and from 3 to 5 cathartic pills and 5 grains of blue mass should be given simultaneously as the first dose. The belladonna mixture is continued every hour of the day and night, and twelve hours after the initial dose the patients are again given from 3 to 5 cathartic pills followed six hours later by a saline, and at the twenty-fourth hour after the initial dose they are again given cathartics and again at the thirty-sixth hour. After these last cathartics the bilious stools appear, and by the forty-fifth to forty-eighth hour castor oil is given. Sometimes it is necessary to carry on the treatment over another period and the cathartic pills and blue mass are again given at the forty-eighth hour, which would bring the end of the treatment about the sixtieth hour. These patients should be trained physically as the morphinists, but they should be carefully looked after for a longer period.

CHAPTER XII

FOOD POISONS

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WHENEVER a given article of food becomes a vehicle for an injurious agent it is for the time being a poison. Such a food *acquires* its poisonous property, in distinction from that which is *always* injurious. In the latter instance we are dealing with plants or animals in which the elaboration of poisonous substances is a normal process, as in certain mushrooms and fish. The poison of such may be said to be of endogenous origin, whereas in the former it is accidentally present, from an outside source, and is therefore exogenous.

Poisonous metals, animal parasites, and bacteria, make up the three chief causes of unwholesome food. Accidental poisoning from metals in the food is the least common, so much so, that in nearly all ordinary intoxications the question of the presence of metals may be disregarded. Nevertheless, notable outbreaks of this nature have been known even in recent years. Thus, the famous "beer epidemic" of Manchester and other English cities, in 1900, was due to the accidental presence of arsenic. Other poisonings, caused by water which had taken up lead or zinc, scarcely need mention. The wide use of canned goods suggest the possibility of these becoming poisonous by the solution of tin or solder, but the small amounts of these in solution could only manifest an action after the prolonged and exclusive use of such foods, a condition which never obtains in ordinary life.

Obviously, the addition of toxic organic substances to food or beverage may lead to poisoning. A wholesale poisoning of this kind occurred in Altoona (1911) from oleo-margarine in the preparation of which Maratti fat was employed. Another example was afforded by the Berlin poisonings of 1912, due to the consumption of cognac prepared with methyl alcohol.

The animal parasites, such as trichina and cysticercus, are also of relatively little importance, especially in comparison with the group of bacteria. The latter constitute the chief factor in poisonous foods. At times, food may be derived from diseased animals, and injurious effects may be directly due to the presence of the specific germ, and the poisoning represents actually an infection. At other times, food may become accidentally contaminated with germs, such as typhoid bacilli, and may give rise to epidemics. And lastly, food may be invaded by bacteria which are themselves unable to grow in the living body but form their poisonous products directly in the food.

POISONOUS FISH

The ill effects following the use of fish (Ichthyismus or Ichthyotoxismus) may be due to a number of causes, some of which are well understood while others are still far from being satisfactorily explained. Obviously, poisonings of this kind are relatively more frequent in countries in which fish form a large part of the diet, notably Russia, Japan, and the West Indies. The several causes may be grouped under four heads. First, the presence of normal or physiological poisons in the fish; second, invasion by animal parasites; third, contamination with metallic or other poisons; and fourth, the presence of bacteria or their products.

1. **Physiological Poisons.**—There are many fish which are always poisonous, while others may become so during the spawning season. The consumption of such fish may lead to severe and even fatal intoxication. Thus, from 1885 to 1892, in Tokio alone, 993 cases of so-called fugu poisoning were reported, of which 680 were fatal—a mortality of more than 68 per cent. At times even, notably in China and Japan, such fish are taken for suicidal purposes. The fugu poisoning of Japan and the East Indian Islands is due to various species of Tetrodon and Diodon. The active agent, which resembles curare somewhat in its effects, is present in the ovaries and testicles. The earlier Japanese investigators designated this substance as *fugin*. Tetrodonic acid and a base, Tetrodon, were isolated by Tabara. The symptoms of fugu poisoning resemble those of curare. There is dyspnoea, cyanosis, dilatation of the pupils, relaxation of the sphincters, paralysis of speech, dizziness, salivation, and vomiting. After the onset of the symptoms death may result in from one to two hours. Prompt administration of emetics and hypodermic injections of strychnine are indicated.

While the organs of the several species of tetrodon are always poisonous, there are other fish which become toxic only during the spawning season. Under these conditions the roe of different members of the sturgeon family, of the pike, and the barbel, have been known to cause pronounced and even fatal intoxications. The symptoms are those of an acute gastro-enteritis.

2. **Animal Parasites.**—Under this head it is sufficient to mention the numerous infections with *Bothriocephalus latus*, directly traceable to the eating of fish infested with the larvæ.

3. **Metallic and Other Poisons.**—Poisoning from canned fish is sometimes ascribed to the presence of tin and other metallic poisons which have been dissolved out by the acid or ammoniacal contents. It is known that appreciable amounts of tin can be obtained at times from canned goods, but that fact in itself is insufficient to explain the effects observed. In all such cases, decomposition of the contents by bacteria offers a more rational explanation.

Some cases of poisoning have been ascribed to the food taken by the fish, such as poisonous medusæ and corals, and decomposing proteins. Without doubt, fish may become infected by eating putrid food or by living in contaminated waters, but when this does occur the resulting

poisoning properly belongs under the head of bacterial poisons. The symptoms, which have been noted in such cases, are those of an acute gastro-enteritis or are of a nervous order.

4. **Bacterial Poisons.**—As might be expected, intoxications arising from this cause are fairly common and occur under various conditions. Thus, the fish may be diseased and the infection transmitted when the flesh is eaten raw. Again, the fish when caught may be perfectly wholesome, but, as a result of imperfect preservation, bacterial contamination may occur with the production of poisonous products. It is necessary, therefore, to consider these two types of infection separately, especially since a similar condition will be noted in connection with other foods.

Epidemics among fish have been repeatedly observed in this and other countries, but it is only within recent years that they have been studied from the etiological standpoint. It is not within the scope of this article to consider such outbreaks except insofar as they throw light upon the subject of poisonous fish. That the consumption of such diseased fish may cause intoxications, and even actual infections, may be theoretically conceded even if such occurrences are few in number. Fischel and Enoch, in 1892, isolated from a carp, which died during a fish epidemic, a spore-bearing bacillus (*B. piscicidus*) which was pathogenic for mice and guinea-pigs. The toxin elaborated by this bacillus was readily destroyed by boiling. From diseased trout, Bataillon, in 1894, isolated a bacillus closely related to *Proteus vulgaris*. It was apparently pathogenic for pike, crabs, and frogs. In the same year Emmerich and Weibel studied another epidemic among trout in which they found a bacillus (*B. salmonicida*) differing from the preceding. Similar observations were made in 1893 by Charrin in connection with a barbel epidemic in the Rhone, and by Canestrini, who isolated from diseased eels a bacillus resembling that of cholera. This was pathogenic for fish and frogs, but not for mammals.

One of the most interesting studies of fish infection is that of Sieber-Schoumow. Two outbreaks occurred among the fish in a palace reservoir at St. Petersburg, in 1894, and on both occasions she isolated an organism which she named *B. piscicidus agilis*. During an epidemic in Lake Zurich, in 1898, Wyss isolated a liquefying bacillus, which he considered to be identical with Sieber-Schoumow's bacillus, and *Proteus vulgaris*. The organism was pathogenic for fish, mice, and guinea-pigs.

The outbreaks mentioned above were not associated with any instances of poisoning in man, though it is reasonable to believe that if the fish had been eaten in a raw or partially cooked condition such results might have followed.

The observations of Arustamow, made in 1891, are usually taken to indicate the effects of diseased fish. He studied eleven cases of fish poisoning of which five ended fatally. These were caused by the consumption of four kinds of fish which were eaten in a raw, salted condition. The fish, though somewhat soft, were of good appearance and showed no sign of decomposition. The process of salting was not very effectual, since the entire bodies were found to be permeated with living bacteria. From the fish and the organs of the fatal cases he isolated four kinds

of bacteria, of which two, however, were particularly studied. Subsequently, these two organisms were studied by Konstansoff, who arrived at the conclusion that the bacillus obtained from the salmon was an ordinary *Proteus vulgaris*, while that isolated from the sturgeon was a variety of the *B. coli*.

The studies of Konstansoff are particularly valuable, inasmuch as they throw new light upon the nature and origin of the fish poison. His material was a sturgeon which poisoned two people. The fish was of good appearance and showed nothing abnormal. All attempts at demonstrating the presence of bacteria, either in stained preparations or by the usual cultivation methods, failed; in other words, the material was sterile. This was due to the fact that the sturgeon was well salted, containing as much as 15.6 per cent. of sodium chloride. Experiments made with ten different organisms showed that when these were planted in broth containing 15 per cent. of salt no growth took place, and, moreover, all died out (spores excepted) in from three to five days. When fish were injected with such cultures and then salted they were found to be practically free from organisms after the twentieth day. As fish are not salted immediately after being caught but are kept for some time and even transported to a considerable distance, it is evident that partial decomposition may set in, especially if the fish were infected or diseased when taken. The subsequent salting inhibits the further growth of such organisms and even destroys them, but the poison which they have already formed persists and can only be removed by boiling.

From Konstansoff's investigations of the conditions under which normal fish give rise to this or a similar toxin, it is certain that bacteria are necessary. In ordinary putrid decomposition of fish various poisonous products are formed, some of which resemble the above toxin while others are of the nature of ptomains. It is generally recognized, since the work of Brieger, that highly poisonous products are to be found only during the first days of putrefaction and that they disappear as this progresses, giving rise to relatively non-poisonous ptomains. In other words, the products of the initial changes, which are hardly recognizable by the sense of smell or taste, are more dangerous than those of advanced decomposition. Konstansoff showed that a uniform distribution of bacteria in the fish, a condition which is best realized when the fish is diseased or septicemic, insures a uniform production of toxin in the tissues. The salting of the fish at this stage arrests all further decomposition, but the already elaborated toxin remains unchanged, and, as a result, such fish, when eaten raw, cause the well-known symptoms of intoxication.

The symptoms observed in this type of poisoning, as well as the properties of the toxin *in vitro*, resemble very closely those of *B. botulinus*, which, as will be shown, produces the most severe type of meat poisoning. The presence of this organism in fish has never been established, and until this is done it will be best to regard these two kinds of intoxication as etiologically distinct. The ill effects after eating such raw fish appear in from ten to twenty-eight hours. The fatal result, when it supervenes, occurs only after several days, and at no time has it been

observed within the first twenty-four hours. The quantity eaten has no necessary relation to the severity of the symptoms. Thus, a small amount may prove fatal, whereas a larger portion may be followed by recovery. This peculiarity is probably not due to idiosyncrasy or to an uneven distribution of the poison in the fish but depends rather upon the quantity of food in the stomach. The dilution caused by the presence of a large amount of other food, and the consequent retarded absorption, may favor the destruction of the poison by the digestive fluids.

Symptoms.—The symptoms due to the fish poison just described are general weakness, dull pain in the abdomen, dyspnoea, mydriasis, impaired vision, diplopia and vertigo, complete dryness of the mouth and tongue, inability to swallow, and loss of speech. Vomiting and diarrhoea are absent and instead there is obstinate constipation and retention of urine. Vomiting is absent at first but may come on in the later stages. There is no rise in temperature and, on the contrary, there may be a fall of several degrees, especially before death.

The other type of bacterial poisoning from fish presents an entirely different train of symptoms. It is of the nature of an acute gastritis and gastro-enteritis. Violent vomiting, excessive diarrhoea, dizziness, tremor, prostration, and cardiac syncope are observed. Autopsy shows extensive follicular enteritis with necrosis, hyperemia of many organs, fatty degeneration of the liver, and toxic degeneration of the heart. These were observed in an instance of fish poisoning at Zurich in which fourteen persons were affected, two of whom died within twelve hours. From the fish and from the spleen and blood of the deceased persons, an organism was isolated which was identified with *B. enteritidis*, an important cause of meat poisoning. This outbreak therefore, unlike the above, is clearly an infection and intoxication.

As poisonous products are found in the raw and imperfectly salted fish it is evident that like substances may develop in canned fish. Indeed, serious results have followed the use of canned salmon, as is reported by Ballard. In spite of the fact that the can was "blown" and the contents partially decomposed, they were consumed by five persons. Three of these recovered, while one who ate the most became ill about ten hours after eating, and died in three days. Another who ate somewhat less died in five days. No organism could be obtained from the fatal cases, or from mice which died after being fed some of the salmon. This would indicate, as in Konstansoff's experiments, the presence of a soluble toxin.

From some canned salmon which caused poisoning in a man, Vaughan isolated a micrococcus which was found to be highly toxic, especially when grown under anaërobic conditions. About twelve hours after eating this fish the patient began to suffer from nausea, vomiting, and a griping pain in the abdomen; and six hours later he was found vomiting small quantities of mucus, colored with bile, at frequent intervals. The pulse was 140, the temperature 102° F., and the respiration shallow and irregular. A scarlatinous rash covered the entire body, but disappeared in the course of the next day; the temperature remained above the normal for four or five days, and eventually complete recovery followed.

Summing up the observations which have been made thus far upon the role of bacteria in fish poisoning, it is evident that many bacteria, especially of the *Colon* and *Proteus* group, take part in the process. The detection of *B. enteritidis* has been mentioned, and it may be added that *B. paratyphosus* B was reported by Wiechert and also by Stoll. An organism of the type of *B. botulinus* may, at times, be expected.

POISONOUS SHELL-FISH

The conditions which render such food poisonous are much the same as those which have been given in connection with poisonous fish. Thus, there is always the possibility that the molluscs may be diseased at the time they are gathered, in which case the infection is transferred to the consumer. The existence of such disease, however, has not been established as clearly as in the case of fish. A second condition is to be found when such food is perfectly wholesome at first, but on keeping, as a result of even slight decomposition, becomes toxic. With this, as with other foods, the initial products of putrefaction are the most dangerous. For example, mussels which have been allowed to decompose for some days have been shown to be free from poisonous substances. It would appear that the first products of the cleavage of proteins and of lecithins are especially poisonous, and that by the further action of bacteria these are then converted into less toxic, or even inert, bodies.

The most important condition which bears upon the toxicity of molluscs is their habitat. It has been repeatedly demonstrated that when these are grown or kept in polluted waters, they acquire toxic and even infectious properties. On being transferred to fresh clean water, they soon lose their poisonous character. The fact that perfectly fresh mussels at times cause severe and even fatal intoxications, would seem to indicate that the elaboration of the poison may occur during the life of the animal. It is because of this that some writers consider such products to arise by tissue metabolism, and hence designate them as "leukomains." Others have expressed a belief in the existence of a distinct poisonous variety of mussel, while still others have held that the mussels had taken up poisonous food material or even metallic poisons. Such views are no longer considered seriously, since the condition mentioned can be accounted for more easily by the known facts regarding the presence and action of bacteria. Molluscs living in polluted waters are known to take up large numbers of different kinds of bacteria which they may maintain in a viable state for a considerable length of time. Without doubt some of these organisms are able to act upon the host, and thus give rise to poisons, but the exact conditions under which these products are formed in the living mussel are as yet undetermined.

Of far more importance than the occasional poisoning from shell-fish is the fact that these convey specific infections to man. It has been established beyond a doubt that oysters and other molluscs are a prolific source of infection. A marked instance is that afforded by the mayoralty banquets which were held at Southampton and Winchester, in 1903.

Of the 132 guests at the former 55 became ill, and all but one of these had eaten oysters; 11 developed typhoid fever. Of 134 guests at the latter place 62 became ill and 10 of these had typhoid fever. The evidence showed that the oysters had been gathered at the same place, from beds polluted with sewage. An examination made by Klein showed the presence of a germ belonging to the *B. enteritidis* group.

Mussels.—Poisoning from the common mussel (*Mytilus edulis*) is by no means rare in England and on the Continent. The symptoms of intoxication are subject to considerable variation. In general three types are to be recognized. The first partakes of the character of a gastro-enteritis. The choleraic symptoms, such as nausea, vomiting, diarrhoea, do not appear until after the lapse of some hours. Death may result, but not as a rule. This type corresponds to similar forms of intoxication caused by meat, cheese, and other foods.

A second type of intoxication presents essentially nervous symptoms, and is the most common form. It begins with a sensation of heat. Itching appears, usually at first in the eyelids, but before long spreads over the face and may involve a large part of the body. A diffuse exudative erythema or general urticaria develops. Angina and dyspnoea are at times pronounced. In this form, recovery usually takes place after a few days.

The third type is paralytic and suggests the action of a curare-like body. It is less frequent and more dangerous than the preceding forms. To a certain extent it may be compared with the intoxication caused by Konstansoff's fish toxin, or with that of Van Ermengem's *B. botulinus*. It differs from these, however, in the rapidity of the onset of the symptoms and in the fact that boiling does not destroy the poison. The apparently perfectly fresh mussel may cause a rapidly fatal intoxication. Thus, in one case the symptoms came on almost immediately after eating boiled mussels and death occurred in fifteen minutes. In another case the mussels were gathered from water known to be polluted, and, although they were washed and cooked thoroughly, in several changes of water, yet they poisoned two persons, one of whom died. Four hours after eating the meal they were seized with giddiness and were unable to stand or sit up. They showed mental excitement or delirium, closely simulating early alcoholism. There was numbness of the extremities, diminished sensation, and dilated pupils. The abdomen was distended and tympanitic; constipation was present. Dryness of the throat, constriction in the neck, difficulty in breathing and swallowing, and a tendency to syncope were prominent symptoms. The temperature was normal, and the pulse did not go over 80. One recovered in two days.

One of the most conspicuous examples of mussel poisoning was at Wilhelmshaven, in 1885, where a large number of dock laborers and their families were affected. According to Schmidtman the symptoms developed shortly after the cooked mussels were eaten, or within a few hours, according to the amount consumed. They began with a feeling of constriction in the neck, mouth, and lips. The teeth were set on edge as if sour apples had been eaten. There was a pricking, burning sensation of the hands, and later of the feet. Giddiness followed but

no headache; a feeling of lightness of the body, with a sensation of flying and general excitation similar to that of alcoholism, restlessness, some anxiety, with slight distress in the chest, were present. The pulse was hard and rapid (80 to 90) without any increase in temperature. The pupils became dilated and reactionless but there was no impaired vision. Speech became difficult, broken, and jerky, and the limbs heavy and stiff. The patients became dizzy, staggered, and grasped spasmodically at objects which they missed, and finally the legs were no longer able to support the body. Then came marked nausea and vomiting but no abdominal pain or diarrhoea; there was numbness of the hands and coldness of the feet at first, gradually extending over the whole body, with a feeling of suffocation; in some cases there was abundant perspiration, followed by quiet, restful sleep. Death occurred in one case in one and three-quarter hours; in a second, in three and one-half hours; and in a third, in five hours, after eating the mussels.

The chemical examination of the poisonous mussels was made by Brieger, who succeeded in isolating several bases or ptomains, one of which (*mytilotoxin*) proved to be highly poisonous. The effect produced by this in animals was the same as that which followed the administration of boiled extracts of the mussels. Therefore, intoxications of this type are due to a heat-resisting alkaloid, or ptomain, and in a sense are analogous to those caused by poisonous mushrooms. The production of the poison, however, is not a physiological one, as in the latter, but the result of the action of bacteria in the polluted water.

In two fatal cases resulting from eating large quantities of raw mussels, the symptoms and pathological lesions were, according to Boinet (1911), those of mytilo-congestine and for that reason he regarded these poisonings as anaphylactic intoxications. While this explanation may hold for isolated cases it can hardly account for the group intoxications, such as the one noted above.

Oysters.—The part played by oysters in the spread of typhoid fever and other infections has been noted, and there remains to be considered the acute intoxication to which they at times give rise. Gastro-intestinal disturbances of variable intensity have repeatedly occurred, due to oysters derived from sewage-polluted beds. The intense poisoning, such as is given above under mussels, is fortunately not a common occurrence. A striking instance is reported by Brosch in which an officer died in twelve hours after eating some oysters which at the time were noted to possess a bad taste. The symptoms began in a few hours with headache, pains in the side, difficulty in swallowing, salivation, impaired vision, and retention of urine. The gait became staggering, deglutition impossible, and speech difficult and indistinct; paralysis of the right side of the face, including dilatation of the pupil and ptosis of the right eyelid, followed. Finally, cyanosis set in, salivation ceased, likewise respiration, while the heart continued to beat for about two minutes. The nature of the poison in this case was not established, but it is suggestive of the botulinus toxin.

Lobsters.—Similar intoxications have been induced by lobsters and crabs. Jaksch cites an instance in which an entire company partook

of lobsters without any ill effects, but the remnants, which were eaten next morning by a family, caused severe illness and two deaths, the early stage of decomposition clearly giving rise to poisonous products. Another illustration is afforded by Georgii, in which a number of young people ate a mayonnaise made from canned lobsters. The symptoms were nausea, vomiting, much pain, severe headache, small, rapid pulse, and a slightly subnormal temperature. Urticaria, eye symptoms, or paralysis, did not appear.

POISONOUS MEAT

The earliest recorded observations regarding poisonous meats were made on sausages, the wide use of which, especially in Germany, frequently led to extensive outbreaks. It became customary to speak of the "sausage poison," and the condition itself was designated as Botulism or allantiasis. A better knowledge of the conditions leading to the production of poison in this food has resulted in a lessening of such occurrences. The sausage is not the only meat food which may acquire poisonous properties. Every kind of meat is subject to the same changes, and if these are more frequent in the sausage it is merely because of the method of preparation and the conditions of keeping.

The question of a physiologically poisonous meat, as in some fish, and the possible presence of metals can be passed by in view of their very infrequent, if not altogether doubtful, occurrence. Similarly, the ill effects from the eating of meat infected with animal parasites, such as trichina and cysticerci, need no special attention here. After eliminating these, the entire phenomenon of poisonous meat resolves itself into the presence of bacteria and their products.

The infection of meat may result in one of two ways: First, the animal may be perfectly healthy and, when slaughtered, yield flesh entirely wholesome and free from bacteria. Such meat can acquire poisonous properties only by the introduction of bacteria from without, by contact with unclean utensils, vessels, and the like. The chopping-up of meat obviously favors the spreading of organisms through the mass. Under suitable temperature conditions, the bacteria thus introduced multiply sufficiently to give rise to poisonous products, and, as a result, what was wholesome meat in the beginning, may be positively injurious. Obviously, under these conditions various species of bacteria may be found, and among these may be some which are true saprophytes, such as *Proteus vulgaris* and *B. botulinus*.

A second source of infection arises when the animal is diseased at the time it is slaughtered. In such a case, a specific pathogenic organism is present, more or less widely distributed in the tissues or organs, and, for that reason, the fresh meat may be toxic, or, at all events, it readily becomes so on keeping. Poisoning from such a source may not only partake of the nature of an intoxication but may also develop into an actual infection. Abundant evidence has been obtained to show that many forms of gastro-enteritis are really food infections, and that poisonous meat plays a very important part in their etiology. Such facts have been

adduced not only with reference to summer diarrhœas but also in regard to paratyphoid infections. A large number of closely related organisms have been isolated from such poisonous meat, and, so far as known means of differentiation are concerned, they are not to be distinguished sharply from the *B. paratyphosus* B. .

With reference to the chemical products elaborated by the bacteria, very little is known, except in a general way. The old view that such intoxications were due to ptomains is no longer tenable, and such basic products play an insignificant or very secondary rôle. The real poisons are essentially of the same character as those of the pathogenic bacteria. They may be divided into two groups according to their behavior to heat. Thus, in the case of *B. botulinus*, a soluble toxin is produced which is easily destroyed by boiling, and in this respect it resembles closely the toxin of tetanus. In the case of the *B. enteritidis*, the soluble products are not materially affected by boiling, and, hence, meat containing such may still be injurious even after it has been cooked. The presence of poisonous products in meat is not necessarily indicated by changes in taste or odor. In the majority of instances, such food is in an apparently perfect condition, and it would seem as if marked decomposition favored the destruction of the poisons formed during the early stages of bacterial action.

Notwithstanding that many different species of bacteria are concerned in the formation of such poisonous products, it is quite impossible to draw sharp differences clinically between the various intoxications. Two forms, however, are sharply contrasted. In the first the central nervous system is affected and the symptoms are therefore characteristic and well marked. Owing to the frequency of this type among the recorded cases of sausage poisoning, Van Ermengem designated it as true botulismus. In the second form of intoxication, the symptoms are gastro-intestinal. They may be of a mild type and of short duration, or of a more severe character merging into an actual infection. Such food poisonings, according to Trautmann, represent the highly acute, whereas paratyphoid fever represents the subacute, form of an infection etiologically due to one and the same factor.

As already indicated, the cause of the ordinary meat poisoning is closely related to that of paratyphoid fever. The majority of the organisms isolated from poisonous meats during the past ten years have been identified as belonging to the paratyphoid group, which is made to include *B. paratyphosus* B, *B. suispestifer* (hog cholera), *B. typhi-murium*, and *B. psittacosis*. These are also frequently designated as constituting the "hog cholera" or "Salmonella" group. By agglutination reactions this group is readily distinguished from a second group of organisms, also frequently found in poisonous meats, known as the Gärtner or enteritidis group, which includes *B. enteritidis* and a number of rat viruses, such as Danysz, Dunbar, Issatschenko, ratin, etc.

Culturally and morphologically, these organisms are essentially the same and for differentiation it is necessary to resort to serum reactions, such as agglutination with the blood of patients or animals, the absorption of agglutinins (Castellani), and complement fixation. Unfortunately,

these tests are really group reactions. They are not always specific or sufficiently distinctive and hence considerable confusion is bound to persist. By the application of these tests Bainbridge believes it possible to distinguish clearly between paratyphoid fever, which he considers to be due to the A and B strains of *B. paratyphosus*, and meat poisoning which he regards as caused by the two organisms, *B. enteritidis* and *B. suipestifer* (hog cholera). The latter view agrees with that of de Nöbele and others.

Botulismus.—This term, originally employed to designate all forms of poisoning caused by sausage, is here used in the sense given by Van Ermengem—namely, a specific intoxication due to *B. botulinus*. This organism was first isolated by him, in 1895, from poisonous ham. Kempner obtained it from the feces of a hog (1897); and in 1900 it was found, a second time, in ham by Römer. Subsequently (1904), it was isolated from poisonous canned beans, by Landmann; and more recently (1912) by Schumacher from ham and from the spleen of a fatal case. The case of poisoning, supposedly from preserved pears, reported by Peck (1910), was probably due to this organism. The presence of the organism in feces, as well as its close resemblance to the tetanus bacillus, would indicate that its natural habitat is in the soil, which readily accounts for its presence in the canned beans mentioned. On the other hand, the organism can hardly be said to have a widespread existence in nature, since in a large series of tests of soil, intestinal contents of animals, etc., Van Ermengem obtained negative results. Intoxications of this type are fortunately very rare.

The outbreak studied by Van Ermengem occurred at Ellezelles, in Belgium, in 1895, and affected fifty persons, of whom three died. Inquiry showed that the poisoning was due to eating one ham. The flesh of the hog at the time of slaughtering was eaten without any ill effects. Moreover, the other ham, although in a decidedly decomposed state, was eaten with like negative result. This non-poisonous ham was in the same cask as the other, which was, however, on the bottom, immersed in a weak brine. A layer of pieces of fat separated the two hams, the lower one being covered by the brine while the upper was not, and being thus exposed to the air, it underwent ordinary putrefaction. The poisonous lower ham was obviously under anaërobic conditions, and the bacterial changes which occurred were of a different type from those in the one above. It was not putrid, but had a sharp odor like that of rancid butter, and though somewhat macerated it was otherwise of good appearance. The taste was said to be bad by those who partook of it.

The symptoms which followed the eating of the suspected ham were those of the typical sausage poisoning. The onset was rather late, the first symptoms coming on from twenty to twenty-four hours, and in some thirty-six hours after the meal. Nausea, gastric pains, and vomiting were the effects first noted. In two instances there was diarrhœa, while in the others there was obstinate constipation, and retention of urine. Visual disturbances developed in from thirty-six to forty-eight hours in all cases. The patients complained of a fogging of the eyes

and were soon unable to recognize persons about them. More or less marked diplopia came on. At the same time there was observed a marked dilatation of the pupils with complete loss of reaction to light, ptosis of both eyelids, and a peculiar stony stare. There was a sensation of burning thirst and strangling; the swallowing of solid food and even of liquids was difficult and led to choking attacks. The mucous membrane of the mouth, nose, and pharynx, was strongly reddened and covered with a thick, viscid secretion which caused violent attacks of coughing, and even of suffocation. In some there was suppression of salivary secretion, and the mucous membrane was dry and shiny. The voice became dull, and complete aphonia was not infrequent. Extreme muscular weakness was general and persisted for weeks. Notwithstanding these severe symptoms the respiration and circulation were unimpaired. The pulse never rose above 90 and the temperature remained normal. Recovery was slow, extending over several weeks and even months. In the fatal cases, collapse, dyspnoea, coma, or wild delirium were observed shortly before death. Autopsy showed a marked hyperemia of the organs and fatty degeneration of the liver.

The *B. botulinus* was isolated from the spleen of one of the patients. The same organism was found in large numbers, though irregularly distributed, in the poisonous ham. It was also obtained from the organs of animals inoculated with suspensions of the latter. Van Ermengem showed that the organism was essentially a saprophyte and incapable of multiplying to any extent in the body. The symptoms, therefore, are not those of an infection but rather of an intoxication, due to the introduction of the toxin produced by the germ in the meat, or culture.

The toxin of *B. botulinus* is soluble, like that of diphtheria or tetanus, and can be used to produce an antitoxin. Leuchs, employing two different strains of this organism, obtained antitoxic sera which behaved differently, since each neutralized only the effect of the homologous toxin.

Decomposed Meats.—While botulism, strictly speaking, is included under this head, it will be best to reserve this designation for the more common decompositions of meat which in the beginning was perfectly wholesome and did not come from a diseased animal. In other words, postmortem introduction of bacteria into sound food has taken place. It does not necessarily follow that food thus infected shall present gross evidence of decomposition, since the organisms may occur in small numbers, or be unevenly distributed through the mass. Contact contamination of this kind with typhoid, paratyphoid, enteritidis and hog cholera bacilli are known. In the ordinary putrefaction of animal foods, poisonous products are not necessarily formed, as is seen from the relative absence of ill effects after eating "high" game, cheese, and the like. The custom of eating fermented, in reality thoroughly putrid fish, described by Mörner for Norway, holds true for many parts of the world. Actual poisoning from such decomposed foods is of very rare occurrence.

The bacteria which have been noted in connection with such poisonings are of the *Proteus vulgaris* and *B. coli* type. The part played by the *Proteus* in fish poisoning has been discussed. Levy, in 1894, isolated a *Proteus vulgaris* from the vomited matter, stools, and from an ice-

chest in which the infected food was kept. A larger outbreak was studied by Wesenberg, in 1897, in which 63 persons were affected by eating the meat from a cow which was slaughtered on account of illness. From the more or less decayed meat he isolated *Proteus vulgaris*. Silberschmidt obtained from a poisonous sausage, in 1899, cultures of *B. coli* and *Proteus vulgaris*. The following year Pfuhl examined a "beef sausage" which apparently was responsible for the illness of 81 soldiers. From this material, cultures of *Proteus mirabilis* were obtained. Schumburg also obtained from a sausage a *Proteus* culture. More recent observations on the presence of *Proteus* in sausages have been made by Gutzeit and by Pergola. It is of interest to note that Zweifel isolated *Proteus vulgaris* from 165 out of 248 samples of perfectly sound chopped beef—a fact which is readily understood when it is remembered that this organism is the most common cause of putrefaction.

Obviously the decomposition of meat products may be induced by other kinds of bacteria. Thus in an instance in Michigan about fifteen persons became seriously ill from eating poorly cured bacon. An examination by the author showed that the meat was permeated by a large coccus which was highly toxicogenic to animals. Cocci have also been found by other observers.

Diseased Meat.—Under this head will be considered those intoxications which are due to the eating of meat from a diseased animal. The invasion of the flesh or organs of the animal by the specific disease germ is intravital and subsequent multiplication may occur in the food, or in the body of persons eating the same. They constitute by far the most common form of meat poisoning and are characterized by more or less severe symptoms of gastro-enteritis.

The *symptoms* may come on at once, but are usually delayed for six to twelve hours. Nausea, vomiting, colicky pains, profuse diarrhœa, and prostration are nearly always present. At times there is erythema and urticaria followed by desquamation, especially of the palms and soles. Albuminuria and catarrhal pneumonia also occur. The mortality is much less than that of botulism. Autopsy usually shows marked gastro-enteritis of a hemorrhagic nature, an enlarged spleen, and congested organs.

Infections of this kind have followed the use of divers meats, especially beef, veal, pork, and horse-flesh. The use of chopped or minced meat, sausages, pork-pies and the like, is more often followed by poisoning than is the use of the whole meat, for the reason that the method of manipulation insures the thorough dissemination of the organisms through the mass. In such cases the animals are often suffering from a septicemia of puerperal or traumatic origin, or from intestinal infections. The majority of meat poisonings are unquestionably due to the eating of the flesh of condemned, that is, diseased animals. The ill effects usually follow the eating of raw or imperfectly cooked food. In some instances, however, even when the food was thoroughly cooked, intoxication resulted owing to the presence of poisonous products not destroyed by heat. The common impression that boiling will destroy the poisonous properties which a food may have acquired does not always hold good.

Although poisoning from meats was noticed at an early date and frequent attention called to it, an exact inquiry was possible only after the methods of bacteriological study had been perfected. The first attempt to work along the new lines was made by Gaffky and Paak, in 1885, in connection with poisoning caused by sausage made from horse-flesh. More than 80 persons developed gastro-enteritis and one death resulted. The evidence indicated that the horse was diseased. Moreover, the sausage was prepared in a most careless manner, since the unused portions were found to be in an advanced state of decomposition. Macerations of the sausage caused death when injected into mice, guinea-pigs, and rabbits, and from these they isolated a bacillus which was closely related to the colon bacillus.

Another colon-like organism, designated as *B. morbificans boris*, was isolated by Basenau, in 1893, from the meat of a cow which was slaughtered while suffering from puerperal septicemia. Later on, he cultivated this same organism from the flesh of animals having perforative peritonitis, puerperal paralysis, and chronic pyemia. This bacillus is believed to be identical with *B. enteritidis*.

Of especial interest is the food epidemic which occurred in 1888, in Frankenhäusen. The source of the infection was a cow which was slaughtered on account of a severe enteritis. Ali told, 57 persons became ill from eating of the meat. Some of these ate it raw, while most of them had it boiled or roasted; three partook only of the broth. The symptoms were those of a severe gastro-enteritis followed by desquamation. Convalescence was long, in the severe cases lasting for two to four weeks. Only one person, who had eaten a large amount of the raw meat, died. He was nursed by his mother who later developed the same symptoms, probably as a result of infection from the discharges. Gärtner cultivated from the spleen of the fatal case, also from the flesh and intestines of the cow, an organism which he named *B. enteritidis*. This organism resembles the colon bacillus in many respects. On feeding, it proved pathogenic for mice, guinea-pigs, and a goat. On injection, it was more fatal to rabbits, pigeons, and a canary, but not to dogs, cats, chickens, and sparrows. The injection of cultures sterilized by heat produced the same effects as did the feeding of such cultures to the susceptible animals. This resistance of the toxin of *B. enteritidis* to boiling is a striking property, and suggests the like behavior of the products of the tubercle bacillus. The heat-resisting intracellular toxin of the colon bacillus studied by Vaughan, affords another illustration on this point.

In the following year Gärtner found a similar organism in another outbreak of food poisoning at Cotta, near Dresden. These observations of Gärtner attracted considerable attention and numerous workers have since then found the same or a very closely related organism.

An apparently typical *B. enteritidis* was obtained by Van Ermengem in 1891 from the outbreak at Morseele, Belgium, in which 80 persons were affected, of whom 4 died. The flesh was derived from two calves which had severe enteritis; one died and the other was slaughtered. The meat was eaten in a boiled or roasted condition, though the isolation

of the germ from the liver, spleen, and intestinal contents of one of the dead, would indicate that the heat was not sufficient to sterilize the food. An identical organism was obtained from the bone-marrow of one of the calves. Feeding or injection of the cultures in mice, rabbits, guinea-pigs, and calves, produced severe and fatal infection. A monkey developed typical cholera nostras, but recovered. Although there were minor cultural differences, Van Ermengem held that it was the same as the enteritidis bacillus of Gärtner, a view which has been confirmed by the subsequent studies on agglutination.

In 1892, Poels and Dhont investigated a poisoning at Rotterdam, where 92 persons became ill after eating the flesh of an apparently normal cow. The bacillus isolated formed colonies which resembled those of the typhoid bacillus; like the latter it did not ferment lactose. The sterilized cultures were poisonous and the living ones were pathogenic for mice, rabbits, and guinea-pigs. A cow which received an intravenous injection of a culture was killed twenty minutes later, and some of the meat after being kept for three days at a low temperature was eaten by 53 persons. Of these, 15 had in a short time headache, colic, and diarrhoea. In the same year, Fischer obtained an apparently true *B. enteritidis* from a food poisoning at Rumfleth. The same organism was also obtained by him from meat which caused poisoning at Haustedt in 1895. Of more than 50 people who ate of the meat, chiefly in the boiled condition, 27 became ill with severe gastro-enteritis. Recovery took place in from three to eight days. The following year Fischer again found *B. enteritidis* in the spleen of a cow which had an inflamed udder. The food poisoning which occurred at Breslau, in 1893, also furnished a related organism (Kaensche). Johne, in 1894, isolated another enteritidis-like organism from a poisoning in Saxony. Scheef obtained apparently the same bacillus, in 1896, from sausage which affected about 150 people.

An interesting case of poisoning at Ghent, in 1895, was studied by Van Ermengem. A sausage made of pork and beef was examined by an inspector, who, on account of its fresh appearance, pronounced it unobjectionable. He himself ate of the raw sausage and others followed the example. They all became sick and the inspector died in five days. The animals furnishing the meat were not known to be sick. Cultures made from the sausage and from the organs of the dead showed a bacillus which could not be distinguished from the *B. enteritidis* or from that of Morseele or Breslau. At the same time Van Ermengem called attention to the similarity which existed between these organisms and that of the hog-cholera group, a fact which subsequent investigations have fully demonstrated.

A further instance of poisoning from pork sausage occurred at Posen, in 1896, and cultures were obtained from a fatal case by Günther. The bacillus differed from that of Gärtner in minor points only. In the same year Silberschmidt studied a Swiss outbreak caused by pork which came from diseased animals. The bacillus isolated was related to *B. enteritidis* and to that of hog cholera, and for that reason he inclined to the view that the flesh of animals sick of hog cholera could cause

food poisoning. Pouchet also, in 1897, described a hog-cholera bacillus as the cause of a poisoning which developed and involved 48 persons.

Since 1898 the agglutination test has been used in identifying the causative organism in food poisonings. Thus, in an outbreak of gastro-enteritis at Aertryck, in Belgium, de Nobele isolated an organism which agglutinated with the serum of the sick persons even in a dilution of one to four hundred. The sera from other diseases and from normal persons had no agglutinating action on this bacillus. Unlike typhoid serum, which retains its agglutinating action for a very long time, the sera of the poisoned persons lost their agglutinating power in a few weeks. Such sera also agglutinated typhoid bacilli more readily than did normal serum. The sera, however, agglutinated in greater dilution (Aertryck) than the typhoid or enteritidis bacilli. The same author, in 1899, studied another case of poisoning at Brugge, caused by pork sausage. The serum from the affected persons agglutinated the bacillus isolated from the meat in even as high a dilution as 1 to 500, but it had no effect on the Aertryck bacillus. The Gärtner bacillus, however, was agglutinated by the sera, but not to the same extent as the bacillus isolated. Subsequently, de Nobele succeeded in isolating essentially the same bacillus from the organs of persons who died at Brussels and Willebroek, after eating smoked horse-meat. The Aertryck bacillus, because of its agglutination reactions, is generally identified with the hog cholera bacillus, a secondary invader in hog cholera. It is essentially distinct from the *B. enteritidis*. Meat poisonings, due to this organism, have been repeatedly observed.

In England, the first application of the agglutination test in the study of these organisms was made in 1898, by Durham, who had occasion to investigate four outbreaks of gastro-enteritis. In the first of these, at Hatton, 185 persons were affected but the cause was not traced to meat of diseased animals. From the liver of a fatal case he obtained a bacillus which was agglutinated by the sera of the sick in varying dilutions, in some even as high as 1 to 1000. The sera also agglutinated the typhoid bacillus in greater dilution than did normal serum. The Günther bacillus, and one from a Vienna case of poisoning, were agglutinated to about the same extent, whereas the *B. enteritidis* was not clumped except by fairly concentrated sera. By making these tests upon different organisms, Durham was able to show that the epidemic was associated with, and probably due to, a variety of the *B. enteritidis*. In the three other outbreaks studied by him the organism was not isolated, but from the behavior of the sera of the sick to various bacteria it was made clear that the cause was essentially the same, that is, a variety of the enteritidis bacillus.

In the Derby outbreak (1902) the cause was traced to the eating of pork pies. No complaint was made as to the taste or appearance of the pies. Furthermore, the more severe cases resulted from the eating of pies which had been kept several days, showing that the organisms at first probably present in small numbers, in the interval had multiplied appreciably. About 210 persons became ill in Derby and its neighborhood and at least 4 deaths occurred. From the organs and intestines

of two of the cases Delepine isolated the *B. enteritidis derbiensis*. This was said to resemble more closely the bacillus of Gaffky and Paak than that of Gärtner. The agglutination of this bacillus by the sera of the sick persons served to establish its causal relation to the epidemic.

During the past ten years an unusually large number of cases of meat poisoning have been reported, especially in Europe. The observations of Gwyn and of Schottmüller on paratyphoid infections have been followed by numerous studies demonstrating the frequency of the so-called paratyphoid food poisonings. The *B. paratyphosus* B, in addition to being the cause of paratyphoid fever, is credited with the causation of about two-thirds of the food epidemics, the remainder being largely due to *B. enteritidis*. It should not be overlooked that these two bacilli in reality represent two distinct groups of organisms, each having an almost indefinite number of varieties. Collectively, they constitute a large intermediate group between the colon and typhoid bacilli. As already indicated, the cultural and morphological properties offer little or no aid in differentiation. It is only by the serum reactions that a separation can be effected. In this way the *B. enteritidis* (Gärtner) and the *B. suipestifer* (hog cholera) are differentiated from *B. paratyphosus* B.

The serum of typhoid fever agglutinates Gärtner's bacillus almost as readily as the typhoid bacillus, which shows that a certain kinship exists between these organisms. On the other hand a typhoid serum of very high potency, obtained by artificial immunization, will distinguish with certainty between the two bacilli. Mention should be also made of the fact that the serum of animals immunized to the *B. enteritidis* agglutinates the typhoid bacillus though in less dilution than its own kind; moreover, it has no action whatever on the colon bacillus.

POISONOUS MILK AND ITS PRODUCTS

Of all the articles of food, milk unquestionably is most subject to bacterial contamination, and, for that reason, it is a most prolific cause not only of acute poisonings but also of real infections. The fact that milk is used to a large extent in a raw state accounts for all such accidents. Certainly, instances of poisoning from boiled milk are wholly unknown. Injurious bacteria present in the milk may be derived from various sources. They may come directly from the diseased animal, as in tuberculosis; or be introduced either by the addition of impure water, or of excretal and other infected matter. It is unnecessary to consider these conditions at length, since in a sense they do not come under the ordinary meaning of the term poisonous milk. And yet, even a passing mention must be given to the part played by milk in the transmission of several diseases—for example, diphtheria and scarlet fever. Similarly, several epidemics of typhoid fever and "sore throat" have been traced directly to its use. Above all else, the milk bacteria are responsible for most of the gastro-intestinal disorders met with during the summer months, especially among infants; whereas the

choleraic conditions among the older people can be traced with equal certainty to the use of other contaminated foods, particularly meats.

Apart from the real infections which have been noted, acute intoxications not infrequently occur. In such instances, the bacteria present gives rise to active poisonous products of which but little is known. The poisonous ptomain which Vaughan first obtained from cheese has been found in milk on several occasions. It must not be supposed that in every milk poisoning the active agent is tyrotoxin, for such is clearly not the case. Milk may harbor a large number of different bacteria, and each of these will form its own characteristic toxin. Among the organisms which have been studied may be mentioned the virulent colon-like bacilli, the *B. enteritidis* and the *B. enteritidis sporogenes* of Klein. Essentially the same organisms are found in toxic milk as are noted in poisonous meat. When such toxicogenic bacteria are once introduced into milk there is but one further condition necessary, and that is a temperature suitable for their development. The warm weather of summer is therefore particularly favorable to the formation of poisonous products in milk.

The usual result of the growth of bacteria in milk is to cause it to sour. It is worthy of note that acute poisoning from sour milk is rather rare, while that from milk which shows no apparent change, in other words, one which has an alkaline or amphoteric reaction, is frequent. This is in accord with the behavior of the enteritidis group of bacilli in milk which is not coagulated but rendered somewhat transparent.

In much the same way that chopped meats and sausages are particularly prone to become poisonous, it is obvious that preparations made from milk, such as ice-cream, frozen custards, and cream-puffs, may become injurious though the original milk was not. A few hours of keeping under favorable conditions of temperature may so force the growth of the few bacteria originally present that the final product may be decidedly noxious. The popular notion that such intoxications are due to the presence of metals or of injurious flavoring extracts has no basis in fact.

The one product of milk which is most prone to cause poisoning is cheese. In fact, cheese poisoning or tyrotoxismus claimed the attention of the early chemists as much as botulism or sausage poisoning. Various theories were propounded, but no satisfactory explanation was possible without a recognition of the part played by bacteria. The accidental introduction of toxicogenic bacteria, and their subsequent growth under favorable conditions, readily account for the phenomena observed. Inasmuch as different bacteria may take part in such changes it follows that different poisonous products may be met with, depending upon the organism at work. Our knowledge of these bacteria is far from being as satisfactory as might be desired. It has been shown by Vaughan and McClymonds that nearly all cheese contains poison-producing bacteria. Thus, the cultures from forty-nine samples of cheese were found to be pathogenic for white rats, rabbits, and guinea-pigs. The colon group was particularly well represented.

The poisonous ptomain tyrotoxin, discovered by Vaughan, was the

first definite product of this kind obtained from such cheese. Le Pierre obtained another basic substance, which, however, was not toxic. Without doubt other poisonous products are present, as in the case of other types of food poisoning and in real infections.

POISONOUS VEGETABLES

The highly nitrogenous animal products are particularly prone to undergo those alterations which render them dangerous to the consumer. Similar changes, however, may occur in vegetable products, though much less frequently, and, as a result, poisonous bacterial substances of different kinds may result. The same organisms which cause meat to be poisonous may give rise to the same effects when they are introduced into vegetable food. The richer such material is in nitrogen, the more likely is it to give rise to poison production, and, on the other hand, with a large amount of sugars or carbohydrates the formation of such products is retarded, if not suppressed. A well-known illustration of this fact is afforded by the diphtheria bacillus, which produces a maximum of toxin when grown on sugar-free media. As a further instance may be mentioned the changes which occur in whey and in whey proteins. In the former, as in normal milk, bacterial action is evidenced by a typical fermentation in which the sugar present is the chief substance acted upon, and consequently no disagreeable decomposition products of proteins form. By contrast, however, a solution of the milk proteins alone—or what is the same thing, a dialyzed whey—will undergo, under exactly the same conditions, a typical putrefaction.

Not infrequently, the ill effects observed in connection with plant food are due to the presence of metallic poisons. The strong acidity of many vegetables may, in canned goods, cause an appreciable solution of tin, lead, and zinc. Ordinarily the amount of these metals thus brought into solution is small and rarely plays a part in the observed intoxication. Criminal carelessness or ignorance is more often responsible for the presence of dangerous quantities of metals in foods.

A third type of poisoning from vegetable foods is due to the presence of plants which are in and of themselves poisonous. Under this head will fall the fairly well-known ergot, vetch, and mushroom intoxications. These must be considered in the briefest manner possible.

Ergot poisoning is practically unknown in this country, but in Europe it still occurs occasionally, although not to the same extent as in former times. The condition is commonly designated as *ergotismus* and its cause is a parasitic fungus, *Claviceps purpurea*, which develops in the flowers of rye and other grains. From ergot, Kobert was able to isolate at least three poisonous substances, sphacelinic acid, cornutin, and ergotinin. More recent investigations have shown that there are other substances present which constitute the real toxic agent. Thus, Jacoby obtained a non-nitrogenous resin, sphacelotoxin, which he regarded as the specific poison. The recent studies of Barger and Dale have shown that ergot and its extracts contain three active principles, viz.—

ergotoxine, *p*-hydroxyphenylethylamine (derived from tyrosine), and β -iminazolyethylamine (derived from histidine). The last two substances are highly poisonous and are formed by the splitting off of carbonic acid from the relatively indifferent amino-acids in the same way that cadaverine results from lysine. Agmatine, another active principle in ergot, is formed in like manner from arginine. The intoxication may have an acute or chronic course and in either type the symptoms may be nervous or convulsive, or else trophic or gangrenous in character. Vetch poisoning, or *lathyrismus*, is a rather rare condition, met with in some parts of Europe, notably Austria and Italy, in northern Africa and in India. The vetch seed is used in the form of flour as a partial substitute for that of wheat. The eating of bread prepared from it is followed by sudden and severe pains in the lumbar region, girdle sensation, motor paralysis of the lower extremities, tremor, and fever. The nature of the poison is not known but it is probably of the nature of a toxalbumose, of which ricin and abrin, the poisons of the castor bean and jequirity seed respectively, are well-known examples.

The ill effects from eating mushrooms are due to mistaking the poisonous for the edible species. One species of the former contains the highly toxic alkaloid muscarin which, with other poisonous constituents, is responsible for the symptoms induced.

A most unusual and severe form of poisoning from vegetable food occurred at Darmstadt, where of 21 persons who ate of a bean salad, 11 died. The canned beans when opened had a peculiar odor but showed no marked decomposition. The symptoms, as reported by Landmann, came on twenty-four to thirty-six hours after eating. Visual disturbances, such as mydriasis, strabismus, and ptosis, were the first to appear. Then followed difficult deglutition and bilateral paralysis. The pulse became greatly increased, respiration superficial, and death resulted in from five to fourteen days from bulbar paralysis. In the non-fatal cases convalescence lasted through some weeks. The symptoms, together with the almost complete absence of gastro-intestinal irritation, led to the diagnosis of botulism, caused by the toxin of the *B. botulinus*. This was confirmed by the demonstration of the toxin and by the isolation of the suspected organism. Cultures made from the salad gave an anaërobic bacillus, apparently identical with the *B. botulinus* of Van Ermengem. The presence of *B. botulinus* in meats is common enough, but this is the first time that the organism and this type of poisoning were observed in a vegetable food. Landmann endeavored to account for its presence by assuming that it was accidentally introduced with bits of meat into the can, as might easily happen about a kitchen. The fact remains that a highly nitrogenous vegetable, as the bean, may be acted upon by the same organism as is found in meats and that the resultant toxin may be fully as active as that formed in the latter.

A similar case of poisoning, in which 11 out of 12 persons died, occurred at Sawtelle, California, and was reported by Peck (1910). Death resulted in from 25 to 65 hours after eating preserved pears. While no laboratory examination was made there can be no doubt, from the symptoms and cause of the intoxication, that the poisoning was due to *B. botulinus*,

or to a closely related organism. This would seem to be the first occurrence of this intensely toxic germ in food other than meat or beans.

Another striking example, apparently due to infected oatmeal, was reported by Ohlmacher.¹ At the Ohio Hospital for Epileptics, in three days, 218 patients became ill and took to bed. The cause of the poisoning was not positively determined, but, by exclusion and elimination, it was finally decided to be a certain batch of oatmeal, which presumably had been contaminated by the dust arising by the removal of a large section of plaster from the ceiling the night before. This ceiling had been exposed to clouds of dust from a dirt road, and to the steam and vapors in cooking. The surface of the plaster harbored *B. coli* and *Proteus vulgaris* and these organisms were believed to be responsible for the poisoning. The symptoms appeared in from about six to eighteen hours. There was chilliness, especially up and down the spine, cold hands and feet; aching of the limbs, with severe headache and sense of pressure in the head; nausea and vomiting in many cases—but not in all; pain in the abdomen, griping and cramps, and profuse watery diarrhoea. There was dizziness, a staggering gait, prostration, and fever, the latter ranged from 100° to 105° F., and persisted for from four days to two weeks. The gastro-intestinal infection which clearly followed the original intoxication would very properly be termed paratyphoid.

The paratyphoid bacillus has been reported as present in poisonous pudding, gruel, beans, noodles, and potato salad. The Gärtner bacillus, *B. coli* and *Proteus vulgaris* have been isolated from similar foods.

Examination of Suspected Food.—It has been customary to look to the chemist for the detection of the cause of a given poisoning. So far as a search for metallic poisons and vegetable alkaloids is necessary, chemical methods must be used. When the action of bacteria can be excluded with reasonable certainty, a chemical examination should be given precedence, especially when the clinical symptoms point to definite substances, such as lead or arsenic. In the great majority of cases of food poisoning, a chemical examination is of no value and should not be undertaken, certainly not until all other methods of inquiry have failed. The reason for this is obvious, since the amount of suspected food is usually small and would be completely used up for the chemical tests, if these are carried out in the beginning.

In order to avoid secondary decomposition the suspected food should be placed on ice until delivered for examination. Chemical preservatives should never be added. As soon as possible, animal experiments and a search for parasitic organisms should be made. The former serve to demonstrate the fact that poisonous properties are actually present in the article suspected, but the results should be interpreted with caution. The material should be fed to animals, and, if necessary, introduced into the stomach by means of a tube. In such feeding experiments, it is well to bear in mind that the action of the poison is more pronounced when the stomach is empty. Macerations of the material in sterile water should be injected into other animals, and in either case,

¹ *Jour. Med. Research*, 1902, vii, 411.

if they die, the indication is that bacteria or their products are probably present. In that event the experiments should be repeated with macerations which have been passed through a Berkefeld or Pasteur filter; also with such after boiling, in order to demonstrate the presence of a soluble toxin, or of heat-resisting products.

At the same time cultures should be made under aërobic and anaërobic conditions, and grown at the temperature of the room as well as that of the incubator. Plate cultures should be made on the ordinary media, and especially on such differential media as Drigalski-Conradi, Endo, Löffler and Russel. The cultures thus obtained are to be compared with those isolated from the animals. Of special importance is the application of the agglutination test to the organisms isolated, for, if the serum of the poisoned person has a selective action on the germ found, it is conclusive evidence of the relation of the latter to the outbreak. An examination for animal parasites, such as trichina, should not be omitted if pork is present in any form in the food under examination.

Treatment.—The treatment in food poisoning must necessarily take into consideration the cause, for it is obvious that the metallic and physiological poisons, as well as the infection due to animal parasites, must be distinguished from the intoxications and infections due to bacteria. As in the infectious diseases, prophylactic measures are of primary importance, since with proper inspection of food products much can be done to restrict the consumption of improperly preserved food or such as is derived from diseased animals. Thorough cooking, while it suffices to destroy bacteria, does not always, or even as a rule, destroy their chemical products and hence cannot be relied upon exclusively. The meat of condemned animals, if it must on economic grounds be used as a food, should never be eaten unless thoroughly cooked.

In the severe intoxications with rapid onset, as those due to shell-fish, free lavage of the stomach should be used as early as possible and followed by a brisk cathartic, such as calomel, gr. ij (gm. 0.13), followed by a saline. Indeed, it is hardly necessary to emphasize the importance in all food poisonings of removing the toxic material by lavage, purgatives, and diuretics except in cases of collapse when stimulants may be required. In the very acute cases, in which death occurs rapidly, there is little that can be done except to employ symptomatic treatment. In the more protracted cases, accompanied with paralyses due to the toxin of the *Bacillus botulinus*, artificial feeding may be necessary, and, if possible, the antitoxic serum for this form of poisoning should be employed, though the results are not very encouraging. In this type of poisoning intestinal lavage should be used. Salt infusions and pilocarpine injections have been recommended.

As the more common food poisonings represent true bacterial infections of the intestinal tract, the use of drugs such as calomel, salol, and like agents is indicated. Opium or morphine may be used to check excessive diarrhœa except in threatened collapse, and the vomiting may be allayed by ice. A liquid diet consisting chiefly of sterile milk and albumen-water is advisable. In the more strictly paratyphoid infections the treatment is the same as in typhoid fever.

CHAPTER XIII

PELLAGRA

By K. HEBERDEN BEALL, M.D.

Synonyms.—Mal de la Rosa; Mal del Sole; Mal del Hgado; Alpine Scurvy; Mal de Misère; Psychoneurosis Măidica, and a host of others, each reflecting the name of an affected region, a prominent symptom, or a fancied etiological factor.

Definition.—Pellagra is an endemic disease of temperate and sub-tropical countries of unknown cause. Its pathology and symptomatology are protean, but it is upon the skin, alimentary canal, and nervous system that its principal manifestations are exhibited. The course is usually chronic, with recrudescences each spring, and an amelioration during the winter months. It may terminate in recovery, temporary or permanent insanity, chronic cachexia, or death.

History.—It is probable that pellagra existed in Europe long before its first definite description by Casal in 1735. The name *pellagra*, a popular one (from *pelle*—skin, and *agra*—rough), was introduced into literature by Frapolli, of Milan, in 1771, and it is certain that at this date pellagra was a common disease in Italy. Conditions in France seem not to have been favorable for pellagra. Having a good beginning in 1829, it flourished moderately for a number of years and then declined, to disappear entirely by 1900. In Austria and Roumania it seems to have a fertile field and is on the increase. The disease is also said to be increasing in southern Russia, Turkey, Greece, Poland, Servia, and Bulgaria.

Pellagra was reported in Egypt in 1847 by Pruner, but little credence was given this report until 1893, when Sandwith showed conclusively that pellagra prevailed extensively in the rural districts of that country. He has also reported cases from South Africa. In 1912, L. Sambon reported the disease endemic in certain parts of the British Isles, namely, Fifeshire, Forfarshire, Aberdeenshire, the Shetland Isles, Essex, and the valley of the Thames. It has been reported in Asia Minor, the Philippines, India, the West Indies, Mexico, and Central America.

The latest invasion of pellagra is that of the United States of America, and a disease which five years ago was of purely academic interest to American physicians, in 1911 killed 410 people and invalidated several thousand more in Alabama alone.

Since its recognition in this country there has been great discussion as to how long it has existed here. J. W. Babcock has published a case history of a patient who was in the South Carolina Hospital for the Insane in 1834, and the full clinical notes by Dr. Davis, the superintendent, give a clear picture of pellagra as we see it today. Probably sporadic

cases of pellagra have occurred throughout the South for a century, but the evidence has not appeared, as contended by some, that the disease has prevailed to any considerable extent until within the last few years. The wide recognition of the disease in this country began in 1907. In that year Searcy reported an epidemic among the inmates of the Mt. Vernon (Ala.) Asylum for Negroes, and nine cases from another Alabama institution. Independently, in the same year Babcock found and reported pellagra in the South Carolina State Hospital for the Insane, and Merrill reported a sporadic case from Texas. In 1908, the Public Health Service did much to educate the profession by the wide distribution of a pamphlet on the subject by Lavinder, and by the end of 1909 the malady had been reported from sixteen States; in 1910, from thirty-three, and to January 1, 1913, cases have been reported from every State in the Union but nine.

Pellagra has been made a reportable disease by four States only, and it is therefore very difficult to know accurately the prevalence of this malady, but a conservative estimate is that there are at least 30,000 pellagrins in the United States. Remembering its history in other regions of the world, it is fair to assume that unless our prophylactic efficiency is enhanced by future discoveries, a certain section of this country will for a century or more pay a fearful toll of health and life to this enigmatic malady.

Etiology.¹—One theory suggested by Casal, in the first description of the disease, is the so-called "corn theory." Marzari, in 1810, gave to this theory its firm foundation, and to him is credited the creating of the school of *zeists*, from *Zea mays*, whose opponents, ever in the minority, have been known as the *antizeists*. All *zeists* are upon common ground in the belief that there is a relation between the occurrence of pellagra and the use of Indian corn as food, and it is a matter of regret that so many enthusiasts have begun their laborious and painstaking work upon this *unproved* hypothesis, true though it may be. The general arguments of the *zeists* are: (1) That pellagra appeared for the first time in Europe soon after the introduction of corn from America; (2) that the disease followed everywhere the extension of corn culture and its introduction into the dietary of the people; (3) that pellagra occurs only among persons or people who use corn extensively as an article of diet; and (4) that preventive measures based upon the corn theory have in a great measure been successful. While agreeing that corn is responsible for pellagra, there is great divergence as to how this effect is produced.

Marzari believed that deficiency in gluten, and therefore its unfitness for food, explained how corn produced pellagra. This theory did not stand the tests which have shown that corn is a good food, rich in fats and protein, and furthermore, it is a staple article of diet in many regions where pellagra does not exist to any extent, notably Mexico. De Giaxa in 1903, attributed the production of pellagra to the action of the colon bacillus on sound corn. However, few now claim that sound maize can

¹ For a full resumé of theories of etiology and a review of the literature see King, Howard D., *Jour. Am. Med. Assn.*, 1910, liv, 859.

ever produce pellagra, and the contention among zeists is as to how spoiled corn produces the disease.

Sette in 1826 was the originator of the fungus theory, believing that the "scimelpige" growing on corn produced a poison from the oil of the grain, and that this poison produced pellagra. Ballardini in 1845 was the first to assert that the cause was a living organism, the *Sporisorium maydis*. The smut of corn, *Ustilago maydis*, was accused by Pari in 1860, and in 1902 Ceni claimed that the disease was an aspergillosis caused by the moulds *Aspergillus fumigatus* and *flavescens*. Later this same author ascribed the rôle of causative agents to toxins elaborated in corn by these moulds, and still later he resuscitated *Penicillium glaucum* to claim for it this important function. Other organisms which have been held responsible for this malady are *Oöspora verticilloides* and *Oidium lactis*.

Most of the zeists, however, are to be found following Lombroso, who in 1872 formulated the "toxico-chemical" idea of pellagra. The theory is this: "In pellagra we are dealing with an intoxication produced by poisons developed in spoiled corn through the action of certain microorganisms, in themselves harmless to man." Finding from experiment that spoiled corn and extracts of spoiled corn produced ill effects when fed to man and other animals, and accepting these effects as analogies of the pellagra syndrome, he set out to isolate the offending substances. From spoiled corn he extracted three substances: a ruby-red oil, a reddish-brown substance which he called *pellagrosein*, and a resinous substance. The *pellagrosein* he found the most toxic, and to it he attributed the greatest part in the production of pellagra. His experiments demonstrate that in fairly large doses *pellagrosein* is poisonous to man and the lower animals, but it is extremely difficult to ally the symptoms which are produced with the disease pellagra. Many students have accepted Lombroso's main idea, and have published the results of much work on the toxins of spoiled corn and the organisms which produce them.

In 1906 Tizzoni announced that he had isolated, from the blood and organs of pellagrins in the acute stage, a bacillus which he called *Streptobacillus pellagræ*. Later he claimed to have obtained this same organism from spoiled maize and from the stools, cerebrospinal fluid, and blood of chronic pellagrins. His work has been repeated by Lavinder and others with negative results, and at the last American Pellagra Conference in 1912 Bravetta denied the existence of Tizzoni's specific bacillus, and stated that Tizzoni had found this organism in *non-pellagrous* blood sent to him by Bravetta, labelled "*pellagrous*."

Harris¹ has produced the disease in the monkey by injecting a Berkefeld filtrate obtained from the tissues of a human subject. This suggests that the cause is a filterable virus or a microorganism which can pass through such a filter.

Neusser saw in pellagra a combination of two factors, corn consumption and indigestion, and believed that the poisonous substance was

¹ *Jour. Am. Med. Assn.*, 1913, lx, 1948.

produced in the alimentary canal through a perversion of its function. Alcohol, he thought, might be a factor by producing a gastro-enteric catarrh. Many good arguments have been brought against the corn theory, especially the occurrence of endemic foci and other epidemiological peculiarities, and the facts that numerous cases have been found in individuals who have never eaten corn, and that corn has been used extensively for years in some regions without the disease becoming prevalent. Lately the antizeists' side of this question has come to the fore, mainly, through the efforts of L. Sambon, of London, who has endeavored to prove a theory, announced in 1905, that pellagra is a parasitic disease, transmitted by the buffalo gnat *Simulium reptans*. His reasons for believing in the parasitic nature of pellagra are good ones, especially the similarity of other parasitic diseases, malaria, syphilis, and kala-azar, likewise his reasons for suspecting it to be insect-borne, but that the buffalo gnat may be the carrier does not appeal to the American student who has seen pellagra in the arid southwest where a running stream does not exist for miles, and where a water-bred insect, as is the *Simulium*, could not possibly be a factor.

Many have called attention to the points of similarity of ergotism, buckwheat poisoning, and beriberi to pellagra, and it may be that the clearing up of the cause of beriberi may aid in the solution of the etiology of pellagra.

FIG. 46

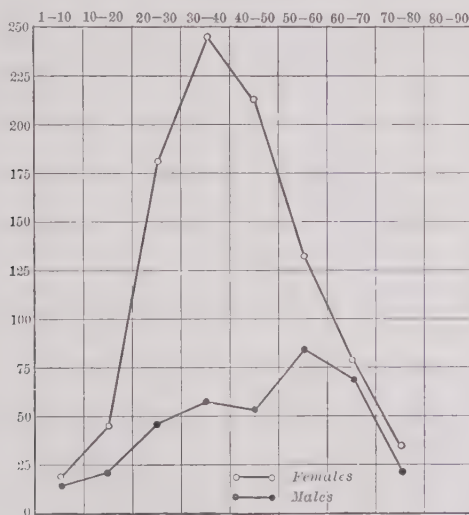


Chart showing relative mortality of pellagra in males and females. Horizontal figures, ages by decades; vertical figures, number of deaths. (Compiled from statistics of Texas State Board of Health for years 1907-1912.)

Predisposing Causes.—Pellagra occurs from infancy to old age, but is most frequent from twenty to fifty. European writers state that sex is of little influence, and according to Procopiu¹ out of 19,796 Roumanian

¹ Procopiu, Georges, *La Pellagra*, Paris, 1903.

cases, 9132 were males and 10,664 females. In America there is a marked preponderance among females. Of 13,829 American cases studied by Lavinder there were 3855 males and 9974 females. Some interesting points are shown in the accompanying chart of 1362 deaths from pellagra in Texas, Alabama, and North Carolina.

A study of a large number of cases convinces us that this mortality chart represents very accurately the comparative morbidity also, as the sexes do not vary in their resistance to this disease. The comparative rarity of the disease among children is evident. In the first decade there is the same incidence in the two sexes, and this is also true of the second if negroes are excluded, negro girls of fifteen to twenty being decidedly more susceptible than the whites. In the third decade there is a sharp rise of the female curve, a further rise in the fourth, and if the negroes are excluded, a further rise in the fifth, then a fall to meet the male curve in the seventh decade. The male curve rises gradually, has a slight fall in the fifth and its crest in the sixth, then it falls and continues parallel to the female curve to the end of life. A discussion of this peculiar sex incidence in this country has been made elsewhere,¹ but it may be ventured here that this comparative immunity among males under fifty, especially white males, the fact that the sixth decade is the most fatal one for white males, and the marked susceptibility of females to this disease is suggestive that one factor in the production of pellagra may be some thing, condition, or occupation which exists in the home or around the house. In Europe, where women share the labor of the fields, this disparity of the incidence in the two sexes has not been noted, and it is interesting that in this country among the negroes the sex incidence is more nearly that found in Europe.

Tentatively accepting the suggestion that one factor in the production of pellagra may be found around the house, Jennings and King have shown that the biting stable fly, *Stomoxys calcitrans*, fulfils better than any other insect the requirements which must be met for an insect to be a potential transmitter of human disease.

Race is of little importance, but Jews certainly enjoy some degree of immunity, which is alleged by the zeists to be due to the slight use of corn by these people.

Pellagra is a disease of warm climates and a change to a cool region usually leads to a rapid improvement in the patient's condition. The disease shows a striking *periodicity*, the symptoms beginning, as a rule, in the spring, lasting for a variable length of time, then declining, to disappear entirely, perhaps, in the winter and be renewed in the following spring. In the United States the greatest number of cases are seen in May and June, and outbreaks of two kinds are seen in the fall, in new cases and in those who have had a spring attack.

That the rays of the sun may excite the erythema of pellagra was shown by Hameau in 1829, but that they are responsible for the nervous and gastro-intestinal phenomena is questionable.

In Europe pellagra is almost entirely a rural disease, and the field

¹ Beall, K. H., "Pellagra in Texas, some Etiological Data," *Transactions of National Association for the Study of Pellagra*, Columbia, S. C., 1912.

laborer is most often attacked. In the United States it is also a rural disease though the urban population suffers to a moderate extent. Of 14,257 American cases tabulated by Lavinder,¹ 9902 lived in the country. Our investigations show that the ideal subject for pellagra in the United States is the country woman of thirty to fifty. However, cases are not uncommon among city people in the best of circumstances, and people of all classes, occupations, trades, and professions are attacked.

Any condition which lowers vitality predisposes to pellagra, though in the majority of cases in which ill health is alleged to have preceded pellagra, this disease existed *unrecognized*. Strambio called attention to the influence of pregnancy and lactation. Procopiu says that alcohol distilled from corn may produce pellagra.

Pellagra is a definite cause of degeneracy in the offspring, but that the disease itself is ever inherited has not been proved. Pellagra is not *directly* contagious.

Until more definite information is available as to the etiology, we must remain ignorant of the length of the incubation period and there will be many ideas to fit the many theories as to etiology. Merk gives nine months; Sandwith says nine to twelve months, while Sambon believes that he has proved the time to be three to six weeks.

Pathology.—The pathological findings are varied, and the true picture is often masked by changes from associated maladies, senility, and alcohol. The characteristic changes are hyperemia, atrophy, and pigmentation. There is usually anemia and cachexia. The body is, as a rule, emaciated and the fat is atrophic and pigmented. Atrophy of the muscles with fatty degeneration and pigmentation, occasionally affecting muscle groups, is very common. Decrease of the compact substance with increase of the medulla leads to a fragility of the bones. Fracture of a rib is a common accident in pellagra, and Bouchard reports a tibia fractured by being struck by a small stone. The most marked lesions are found in the central nervous system, skin, and alimentary canal.

The meninges of the brain are thickened, opaque, and often œdematous, especially the pia. Hydrops of the ventricles is common and the gray matter of the brain is sometimes injected, sometimes œdematous. Microscopically, there are degenerative changes in the nerve cells, principally the large chromophilic cells of the cortex. These cells are swollen, pigmented, and vacuolated; the nuclei are gone, atrophied or displaced. The cell processes are broken or have disappeared; the small cells are less affected. The bloodvessels show fatty degeneration and calcification of the intima, with pigmentary deposits in the adventitia. Atrophy of the cerebrum is sometimes found in marked mental cases of long standing. The meninges of the cord show the same changes as those of the brain. A leukocytic infiltration and an acute meningomyelitis have been described by Belmondo in typhoid pellagra.

As to the primary nerve lesion there is a difference of opinion. Marie, Tuezek, and Marinesco contend for an endogenous lesion, and believe that it is in the gray matter of the brain and cord, and that the changes

¹ "The Prevalence and Geographic Distribution of Pellagra in the United States," *Public Health Reports*, vol. xxvii, No. 50.

in the white matter and the peripheral nerves are secondary. Righetti, Babes, and Sion believe in the exogenous nature of the brain and cord lesions, that they are secondary to a polyneuritis. As Procopiu remarks, the endogenous origin accords with the clinical picture, in which the psychoses usually antedate the paralyses by a considerable period. The nature of the cord changes resemble those of tabes, consisting principally of a shrinkage and atrophy of the nerve fibres with an overgrowth of neuroglia poor in nuclei, and a thickening of the bloodvessels. As emphasized by Babes it is only in advanced stages that a marked resemblance to tabes begins. Degenerations of the columns of Goll and Burdach are found which are similar to those of tabes, with this distinction, pointed out by Lombroso, that in tabes the lumbar cord suffers most intensely, while in pellagra it is the cervical and dorsal. Lissauer's tract and the anterior root zone are sometimes found involved, though not as often as in tabes. Clarke's columns are always affected. The cells are swollen, often without nuclei, the centres being occupied by a coarsely granular pigment mass, and the periphery filled with pale chromatin. In several cases Babes and Sion found a pathological process extending from the posterior roots to the posterior horns; in one case considerable thickening of the bloodvessels; in another, considerable thickening due to a sclerosis in the posterior roots; in other cases granulation tissue surrounding the bloodvessels extended from the posterior roots into the posterior horns. Irregular degenerations occur occasionally in both horns of gray matter. Many changes in architecture have been described: obliteration or doubling of the central canal, isolated areas of gray matter in the white, displacement of whole groups of cells, Clarke's columns being sometimes found in the anterior horns. Babes insists that these anomalies occur in pellagra far more often than under any other condition and suggests that such abnormal relations, confessedly congenital, may predispose to pellagra.

The peripheral nerves do not often show changes, but that some changes have been described is not surprising when we remember their great frequency in chronic diseases. The spinal ganglia are often rich in connective tissue and, says Babes, one often sees unaltered nerve cells surrounded by newly formed nerve fibre nets. The cells of the large sympathetic ganglia, like the cells of the central nervous system, contain considerable pigment. Numerous stellate cells are found in the abdominal sympathetic and the plexus of Auerbach, but the absence of pigment in these structures is notable.

The *erythema* of the skin is trophoneurotic in origin. Besides the erythema there may be hemorrhage and purpura. Microscopically, there is œdema, infiltration of leukocytes and a proliferation of epithelium. There is a hyperkeratosis of the outer layers and the deep layers show a deposition of a large quantity of yellow pigment.

In some cases there is an increase in the number of papillæ, in others a diminution. The sweat glands are rich in cells and contain metachromatic granules. The sebaceous glands are dilated and often show many colonies of bacteria. In old cases a sclerotic process ensues and the normal structures of the skin are destroyed.

The mucous membranes often show trophoneurotic changes. This is especially true of the mouth and pharynx where there may be hyperemia, vesicles, and ulcers. There is often marked gingivitis and sometimes destruction of the gum edge. The tongue may be swollen, fiery red, and raw, with exfoliation of the epithelium and exposure of the papillæ, a scalded appearance. The tongue, however, is sometimes small; there is epithelial atrophy with a reduction in size of the papillæ. Sometimes there is a purpura, and not rarely a secondary infection. Similar lesions are found in other places, especially the rectum and female genitalia. Gangrene of the mucous membrane of the vagina occurred in one of our fatal cases.

The stomach is often normal, sometimes hyperemic, and in rare instances ulcerated. The intestine is usually pale with thin walls due to atrophy of the muscular coat. Ulceration of the large intestine, especially of the rectum, is not uncommon. Sometimes the surface of the intestine is covered by a pseudomembrane due to a necrosis of the superficial layers of the mucosa.

The heart is often dilated and brown atrophy of the muscle is common. The striations are indistinct and considerable yellowish-brown pigment surrounds the nuclei. Sclerosis of the aorta is usual in long-standing cases of pellagra. Aside from many terminal lesions the lungs show fatty degeneration and pigmentation.

The liver is usually small, markedly pigmented, and shows cirrhotic changes. Fatty degeneration and a hypertrophic change are occasional findings. The spleen is reduced in size even in typhoid pellagra. It is sometimes hyperemic and usually contains a great amount of deep-yellow pigment. When malaria is associated, as is not uncommon, the spleen is hypertrophied. Rarely are the kidneys normal. Often they show cloudy swelling, sometimes cellular degeneration and interstitial change. Pigment masses are found in the epithelium of the tubules which often contain hyaline casts. Lombroso found the weight of the kidneys diminished in forty out of fifty autopsies.

The most common complications are tuberculosis, uncinariasis, malaria, and amœbiasis.

Clinical Course.—Pellagra is an insidious disease subject to remissions and exacerbations, and to any description many exceptions may be taken. The disease is usually divided into four periods or stages according to its severity: prodromal, first, second, and third stages, and very roughly the last three stages represent the erythematous, digestive, and nervous stages, each characterized by the predominance of symptoms on the part of the skin, alimentary canal, or nervous system respectively. There can be, however, no set rule as to the sequence of these stages. One case may be markedly neurotic from the start and the whole syndrome for many years be filled with purely neurological phenomena; another may suffer with periodic indigestion or diarrhœa over a long period while he remains in perfect mental equilibrium; while yet a third may have been in apparently perfect health until the appearance of the characteristic eruption. Usually these stages or types fade into each other, and most cases present alimentary and nervous symptoms

at the time when the skin lesion appears to suggest or confirm the diagnosis of pellagra. It is to be remembered that these divisions imply nothing as to the duration of the malady, nor is it necessary that a patient advance regularly through these stages; he might in one year suffer severely from the triad of symptoms—the second or third stage, and return the next year with a well-balanced nervous system, complaining only of a slight digestive disturbance and the erythema.

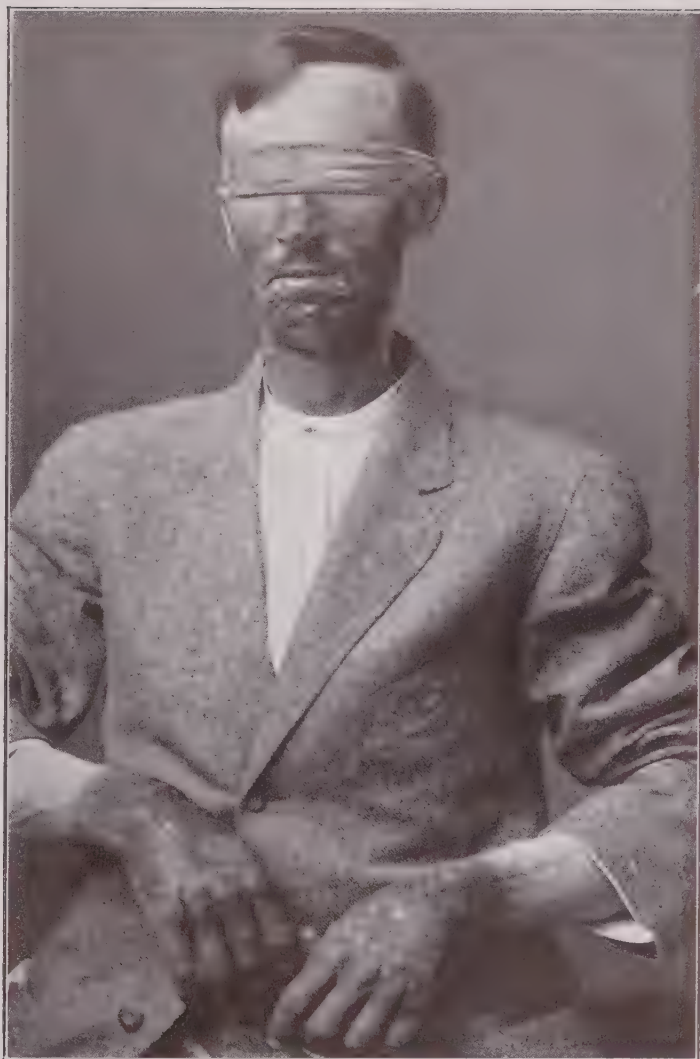
The first symptoms and the exacerbations usually begin in the spring, less often in the summer, and rarely in the fall. New cases are very rarely observed during the winter, and practically all cases begin to improve with the onset of cool weather, while some are restored to apparently perfect health. Another spring, another acute outbreak, and the pellagrin begins again the struggle, perhaps to succumb early, perhaps to hold out until fall, or winter may save him to renew the fight in still another spring.

Usually the patient has difficulty in giving the exact date of the beginning of his ill health. Vertigo, a sensation of burning (feet, hands, stomach, gullet, mouth or any part), insomnia, and slight indigestion are the chief prodromal symptoms. There may be a general lassitude, malaise, cephalalgia, and paresthesias, and many vague nervous symptoms are complained of over long periods of time. The mucous membranes of the mouth are reddened and the flow of saliva may be increased. Procopiu says, that the salivation is due, not to reflexes from the lesions of the mucous membranes of the mouth, but to the action of the poison on the salivary gland or upon the nerve centres. The saliva has usually a salty, disagreeable taste. Often a mild dyspepsia precedes the definite onset, or a mild depression may be the first symptom.

First Stage.—The prodromal symptoms become exaggerated and gastro-intestinal disturbances are more marked. There is anorexia, but rarely bulimia. Usually, but not necessarily, the characteristic stomatitis appears. There is great hyperemia and swelling of the mucous membrane with exfoliation of the epithelium. The tongue is fiery red and raw, and appears scalded; its papillæ are prominent; vesicles, ulcers, and fissures appear, and it is with this that the most marked salivation occurs. A half-gallon of clear, watery saliva was excreted in twenty-four hours by one patient under observation. A common site for ulceration is at the frenum beneath the tongue. Occasionally a fibrinous exudate is formed around the edge of the tongue, under it, and inside the cheeks. This exudate resembles the chicken-fat exudate seen in recent pleurisy, and because of this exudate the diagnosis of diphtheria has been made. Babcock has called attention to a sharp line of demarcation of the stomatitis which often occurs in the roof of the mouth about the line on the hard palate to which the edge of a plate for false teeth extends. An involvement of the mucous membrane of the throat and œsophagus may occur, likewise of the rectum and the genital organs, especially in women.

Dyspeptic symptoms occur, flatulency, fulness after eating, epigastric pains, nausea, and perhaps vomiting. While nausea is common, vomiting is a rather serious symptom. Diarrhœa is frequent, but constipa-

PLATE XIV



Pellagra in an Adult, Showing the Pellagrous
Erythema.

PLATE XV



Showing Symmetrical Erythema Extending up the Forearm.

tion may be present. The diarrhœa is resistant to treatment, and is almost independent of the quality or quantity of food taken. Often it is nocturnal and may be remittent or intermittent. The stools are watery, brown, green, or gray, usually contain mucus and sometimes blood. The diarrhœa is painless, but occasionally there are griping pains and tenesmus.

There is a progressive muscular weakness, especially of the legs, and a gradual loss of weight. The temperature is normal or subnormal. The pulse is usually accelerated, a point which has been neglected by most observers. Vertigo persists and is often the most distressing symptom. Venesection, Roussel states, was a popular remedy for this symptom fifty years ago. The sensation of burning, usually in the region of the stomach or of the feet or hands, but which may affect any part of the body, is an almost constant symptom. Insomnia, sometimes due to headache, neuralgias of various kinds, trifacial, sciatica, etc., are frequent, as are cramps and numbness in the extremities. Irritability, sensitiveness, mental depression, and slight mental weakness may occur. The knee reflexes are usually exaggerated. Slight exophthalmos and widening of the pupils are common. Amblyopia, hemeralopia, and diplopia are rarer eye phenomena. Pellagra is a recognized cause of cataract, especially in children.

Though perhaps unnoticed or unheeded, the characteristic erythema occurs, usually on exposed parts of the body, and is symmetrical in its distribution.

Second Stage.—The symptoms of the first stage persist but increase in severity, and to these are added new symptoms on the part of the nervous system, so that serious physical and mental disturbance is evident. The erythema recurs, perhaps more severely, and following repeated attacks the skin of the hands becomes thickened, and the epidermis dry, rough, and of a yellow, brown, or black color. Occasionally fissures produce a resemblance to the skin of a crocodile. The stomatitis is perhaps more severe, and may be distressing. Often the salivation prevents articulation, and the inflammation may interfere greatly with the taking of food. Like the erythema, the stomatitis is transitory, usually lasting three or four weeks, leaving the tongue smooth and shiny.

The acidity of the gastric juice is diminished and in many severe cases there is a complete absence of hydrochloric acid. The stomach symptoms are aggravated, and vomiting, of more serious import than diarrhœa, may occur. The diarrhœa is more severe, of longer duration, and less amenable to control than in the first stage. Proctitis is very common. Leucorrhœa, painful vaginitis, and vulvitis are annoying features. Amenorrhœa occurs in about one-half of the females, and menorrhagia is often seen, especially in multiparæ. Pellagra frequently leads to abortion.

There is considerable loss of weight and strength and the nervous symptoms are no longer vague. The mind is gradually enfeebled and the depression of spirits becomes a true melancholia. Maniacal outbreaks may supervene and the patient may attempt suicide. Delusions, usually self-accusing, are common; a systematized monomania

(paranoia) is never seen. The sensory phenomena are varied and numerous; the most common, most marked, and most persistent is the sensation of burning which often becomes intolerable, interferes with rest, and has driven patients to suicide. Formication, numbness, and tingling, hot and cold flashes, the girdle sensation, and a dragging sensation in the rectum and genital organs are very common. Anesthesia does not occur. Vertigo may be extreme and lead to a drunken gait, and often there is a sensation of falling forward or backward. Tremors, cataleptic phenomena, and epileptiform seizures often occur. The knee reflexes are usually exaggerated, and as a general rule their diminution in marked cases means serious cord involvement. The Babinski phenomenon was present in 13 out of 100 cases studied by Siler and Nichols. Cramps in the extremities, of isolated muscles or muscle groups, occasionally occur.

Third Stage.—Gradually the anemia becomes a cachexia, the muscular enfeeblement a paralysis, and the mental waverings a dementia. In many cases a paraplegia occurs, and there may be relaxation of the sphincters. Diarrhœa is usually persistent; it is, as a rule, painless, serous in character, and uncontrollable. Cardiac weakness becomes evident and the features of broken compensation may appear. Purpura is not uncommon at the close. Death is usually from marasmus or an intercurrent affection.

Typhoid Pellagra.—At any time, but usually only after several attacks, there may be an aggravation of all the symptoms, especially the mental, and the patient passes into an adynamic condition resembling somewhat severe typhoid fever. This condition bears no etiological relation to the disease typhoid fever. The temperature is usually high with morning remissions but all the other phenomena of typhoid pellagra may develop and death ensue without any rise of temperature. The entire musculature is in a state of tonic contraction and the rigidity is evident on passive motion. Spontaneous movements are tremulous and incoördinate, and irritation may lead to convulsive seizures, local or general. The tendon reflexes are exaggerated and an ankle clonus is not rare. There is a low delirium, subsultus, and occasionally opisthotonos. The speech is drawling and the voice tremulous with a nasal quality. The pulse is rapid, small, of low tension, and there may be evidences of circulatory failure, as œdema of the extremities, ascites, or hydrothorax. The spleen is not enlarged. The abdomen is distended and there are frequent involuntary stools. Excoriations around the anus and genitals, decubitus ulcers, and purpura are often found. Typhoid pellagra usually ends fatally in from one to three weeks.

The Pellagrous Erythema.—The importance of the eruption is chiefly diagnostic; it is of the same significance in this disease as is the eruption in smallpox, scarlet fever, and measles, for when the skin lesion is typical, and it is usually so, a diagnosis may be made from this feature alone. That the rays of the sun may excite the skin eruption is suggested by its appearance principally upon the uncovered portions of the body, and this has been proved by numerous experiments with fenestrated gloves and other skin coverings. However, that other factors have influence

is shown by its appearance on the elbows, under the breasts, around the genitals, and in other situations protected from the light.

The usual time of the appearance of the eruption is in the late spring or early summer. It may appear in the early spring, late summer or fall, but winter outbreaks are very rare. Two, rarely more, separate attacks may occur in one year, although this is uncommon, but acute processes upon old or unhealed lesions are often seen. The erythema usually appears suddenly in the form of sharply circumscribed, rose-red macules of varying size up to three centimeters in diameter. The color disappears on pressure and reappears immediately when the pressure is removed. There may be a slight sensation of itching or burning, but the subjective symptoms are usually absent. After one to several days the spots either disappear, perhaps with slight desquamation, or develop into the typical eruption.

Dry form. The macules may remain discrete, more commonly they fuse; the skin becomes moderately swollen, darker in color, and takes on a peculiar tint, variously described as blue, purple, plum, chocolate, brown, or black. A sharp line of demarcation from the surrounding skin is characteristic. Associated with the swelling there may be disagreeable sensations of tension, burning, or itching. After a variable time desquamation begins, leaving, when complete, a pigmented area to mark the site of the eruption. *Wet form.* Beginning as the dry form, vesicles and bullæ, and following these fissures and ulcers, make their appearance, and with associated infection, occasionally hemorrhage, a distressing condition results. This wet form is usually associated with more severe constitutional symptoms, and while less common than the dry form, is more common in America than in Europe. It is sometimes known as *pemphigus pellagrosus*.

The most constant characteristic of the eruption is *symmetry*, and a skin lesion which has not its counterpart, symmetrically placed on the opposite side of the body, is *almost* surely not pellagrous. Following repeated attacks the skin becomes thickened, is markedly pigmented, usually has a bronzed appearance, is hard, inelastic, and rough. After

FIG. 47



Child of four years with lesions on head and neck, arms and hands, penis, knees and feet.

repeated attacks the skin may undergo atrophy, become thin, and, parchment-like, and occasionally show whitish spots like vitiligo.

The erythema shows a predilection for certain regions, which in the order of the frequency with which they are affected are: the back of the hands ("pellagrous glove"), the most common site, elbows, feet ("pellagrous boot"), face ("pellagrous mask"), neck ("Casal's neck-band and cravat"), genitalia, and knees. Any region of the skin may be involved and a universal distribution is occasionally seen. Merk¹ analyzed 2179 cases as to the distribution of the lesion as follows: 1679 or 77 per cent. the backs of the hands alone; 283 or 13 per cent. the backs of the hands and the neck; 164 or 7.5 per cent. principally on the neck, and 53 or 2.4 per cent. on other parts of the body. Upon the backs of the hands the erythema may be in discrete patches with normal skin intervening; usually, however, the whole surface is covered, the process stopping sharply at the lateral and mesial borders, and extending up the forearm to a variable extent, usually higher in women. The palms are rarely involved, though usually the flexor surface of the wrist or forearm shows the eruption which completely encircles the member at this point. The eruption upon the elbows is commonly most marked over the olecranon processes, and it has often been observed that it appears only after the patient takes his bed, and in such cases is probably a pressure phenomenon (Bass). Upon the face it is of one of two types, discrete or diffuse. The familiar butterfly shape extending to either side of and over the bridge of the nose, and symmetrical lesions on the forehead, cheeks, lips, and chin are often seen; rarely are the ears or eyelids involved. In the diffuse type the whole face is covered except a thin area next the hair line.

The nails occasionally show changes; they may become brittle, of a whitish or grayish color, and may have a fluted appearance.

The pellagrous eruption is to be differentiated from sunburn, eczema, erythema multiforme exudativum (Hebra), and, in long-standing cases, from vitiligo.

Blood.—Moderate anemia is the rule, and the color index is about one. The red corpuscle count is usually about 4,000,000, and the hemoglobin about 80 per cent. In some cases anemia is marked, but counts below 2,500,000 are extremely rare. Anisocytosis occurs in about half of the severe cases; in a few it is as marked as in pernicious anemia. Poikilocytosis occasionally occurs, but is never striking. Nucleated reds and polychromatophilia are extremely rare. The leukocyte count is normal in the absence of complications; with infection of the skin or mucous membranes and in typhoid pellagra a leukocytosis is found. An absolute lymphocytosis is common, but, as pointed out by Buhlig,² this may be connected with the involvement of the mucous membrane of the intestines and reflect nothing of the disease itself. The platelets are not affected.

Urine.—Often there are slight departures from the normal, as a diminished acidity, low specific gravity, 1.005 to 1.015, and occasionally a

¹ *Die Hauterscheinungen der Pellagra*, Innsbruck, 1909.

² *Bulletin Illinois State Board of Health*, 1909, vol. v, No. 7.

diminution in quantity. A trace of albumin is occasionally found, though it is usually absent, even in advanced cases. Hyaline casts are not uncommon, especially in the aged. Indican is found more often than in health. Acetone and diacetic acid are common in cases with marked gastro-intestinal features.

Pellagrous Insanity.—Nervous phenomena occur in all cases of pellagra, and in 5 or 10 per cent. of the cases there is insanity. Ever protean in its manifestations, a great variety of psychical phenomena are exhibited, but the most common psychosis is amentia with stupor, mutism, and a melancholy delirium. The insanity may be acute or chronic, and may take one of many forms, simulating most of the common varieties of mental disease. However, a systematized monomania (paranoia) is almost never seen. An initial delirium may be the first recognized symptom but it is usually only after several attacks that reason fails. Acute outbreaks often occur in the course of chronic pellagrous insanity, and in these periods of excitement (mania or exaltation) homicide or suicide may be committed. Hydromania, or suicide by drowning, is peculiarly common in pellagra, and is thought by many to be provoked by the intolerable sensation of burning which torments the sufferers. Others, believing that pellagra is common only among those who live near streams, allege that drowning is simply the most convenient method of ending existence. Religious mania is common, especially among women. Pellagrous insanity is usually a progressive, but remittent amentia, which unless recovery or death supervenes, eventually terminates in dementia. The dementia, occurring as it does late in the disease, is usually coexistent with the characteristic cachexia and the various paralyses.

Pseudo-Pellagra.—This term which is common in European literature, especially the French, was introduced by an ardent zeist, Roussel, in 1866 to include those cases which were clinically pellagra, but which gave no history of corn consumption. It has no scientific foundation and should not be used.

Pellagra sine Pellagra.—Strambio, a hundred years ago, designated his cases of pellagra without skin lesions as *pellagra sine pellagra*, and this term is still used with the same significance. Some contend that there is no pellagra sine pellagra, but without question pellagra may exist for years without an involvement of the skin. However, the diagnosis of *pellagra sine pellagra* should be in most instances only a tentative one.

Diagnosis.—Well-developed cases of pellagra offer absolutely no difficulty, but in the absence of the erythema or the pigmentation subsequent to it, uncertainty must exist. Often under these circumstances pellagra may be strongly suspected, especially if a stomatitis is or has been present. The important characteristics of the erythema are: seasonal recurrence, a predilection for certain areas, an almost absolute symmetry on the two sides of the body, a sharp line of demarcation from the surrounding skin, and its resemblance to a solar erythema. The backs of the hands in old people, especially men, are often rough and discolored, but the persistence of this condition and the absence of

a sharp line of demarcation should prevent confusion. Occasionally in *pernicious anemia* the pigmentation of the hands, especially if diarrhœa be present, may suggest pellagra, but a blood examination will exclude this malady. Chronic *alcoholism* with the erythema which occasionally occurs may be differentiated by reference to the important characteristics of the pellagrous erythema. Early in its course pellagra is usually confused with *neurasthenia* or *nervous dyspepsia*. Important points of differentiation are: recurrence of spring attacks, the prominence of vertigo and sensations of burning, which are characteristic of pellagra. In such cases the stomatitis suggests and the erythema establishes the diagnosis. Various mental diseases may be simulated by pellagra and the erythema may be essential for a differentiation. Ergotism, lathyrism, beriberi, acrodynia, scurvy, and amœbiasis may show similarities to pellagra, but a close study will reveal many points of distinction. The erythema is essential for a distinction from *sprue*. *Typhoid pellagra* may be confused with alcoholic wet brain, uremia, diabetic coma, or an acute infectious process; in such cases the history is all important, and with the clinical phenomena the diagnosis is usually not difficult. The chief diagnostic features of pellagra are: chronicity with spring or summer exacerbations and amelioration during the cooler months; a characteristic erythema, also periodical; inflammation of mucous surfaces, especially stomatitis, vaginitis, and proctitis; gastro-intestinal features, most commonly diarrhœa; vague nervous symptoms with vertigo and sensations of burning; loss of weight and strength; moderate tachycardia; amentia with mutism and melancholy delirium; and finally, pigmentation of the skin following repeated attacks of the erythema, cachexia, and dementia.

Prognosis.—This is always more or less serious. When a disease appears in an untried region it exhibits an unusual virulence, and this has been the history of pellagra in America. However, even now the American type is less fulminating than a few years ago, but still it greatly exceeds in severity the same disease in its old home. Exact figures cannot be given, but in Europe the mortality is around 10 per cent., in America, 30 per cent. A consideration of the nervous system is most important in prognosis. Pellagra is a destructive disease and destroyed neurones do not regenerate, and while the disease may at times be completely arrested, a pellagrin who has suffered destructive processes in his nervous system cannot be restored to perfect health. Early cases often recover, perhaps completely, and the cure is fairly easy; in the second stage, the cure is more difficult, recovery not so frequent, and often scars are left upon the psychic and somatic nervous systems; in the third stage, recovery is extremely rare, and any improvement comes slowly. Acute or typhoid pellagra is very fatal, but recovery occasionally occurs. Except that the wet form of the erythema usually indicates a more severe type, no information of prognostic value is to be obtained from the skin. Amelioration of symptoms associated with a gain in weight is a favorable feature. Little may be inferred from an improvement during the cooler months, and all pellagrins, "cured" or otherwise, should be closely watched during the spring and summer. Complications,

such as tuberculosis, syphilis, pneumonia, amœbiasis, alcoholism, etc., add to the gravity of the disease.

Treatment.—The present state of our knowledge does not permit a discussion of definite prophylactic measures. The Italian government has accepted the corn theory, and since 1879 has rigidly enforced laws directed against the importation, sale, or grinding of spoiled corn. In addition it is obligatory upon every pellagrous province to provide suitable nourishment for its pellagrins, and to supply these patients and their families with a certain quantity of salt, which is thought to counteract the bad effects of a corn diet. The yearly allowance of salt is seventeen and a half pounds for an adult and eleven pounds for a child. The government and other zeists claim that great good has come from these prophylactic measures, but Sambon and other antizeists urge the failure of these measures as a strong argument against the corn theory.

Of general measures, rest is of the greatest importance and should be insisted upon. A modified Weir Mitchell rest cure should be employed in most cases, and even early cases with the mildest symptoms will profit by a period of rest in bed and freedom from annoying influences. Care should be taken that no mental or physical strain or fatigue interrupts convalescence.

The *diet* should be full and nutritious, and contain considerable quantity of animal protein, care being taken also that sufficient fat and carbohydrate are included. Eggs and milk are of especial value, and many, following Bouchard, have depended upon a strict milk diet, which, however, is not recommended. Whatever may be the opinion as to the relation of corn to this disease, the patient should be given the benefit of the doubt and we should forbid the eating of corn or of any of its products. The dietary should be adjusted to meet the needs and tastes of each patient, but a point to be emphasized is that the presence of diarrhœa should not suggest a limitation of the quantity of food; such a procedure would have little or no effect upon the diarrhœa and the patient would needlessly suffer from malnutrition. Abundance of salt is advised by the Italians.

Hydrotherapy is of the greatest value; warm or cold baths, packs, and douches may be used with benefit. Massage and salt rubs are of service, especially during convalescence.

Psychotherapy should not be neglected, for like rest and forced feeding, it is fully as important in this malady as it is in psychasthenia and neurasthenia.

Fresh air is essential, though exposure to the sunlight is not advisable. Pellagra is, as a rule, inactive during cool weather and pellagrins should, if possible, go to a cool region, there to remain until the weather is cool at home. When this cannot be done because of the patient's condition or for other reasons, strenuous efforts should be made to mitigate as far as possible the effects of the heat. The room should be the coolest, and fans, cold sponges, and ice applications should be employed. Ice applications to the head and abdomen are sometimes of the greatest value.

There is no specific for pellagra, though *arsenic*, introduced by Lombroso, is accredited with such virtue by many. Fowler's solution to

toleration may be used, or one of the newer preparations which are administered hypodermically, atoxyl, soamin, sodium cacodylate, and salvarsan. The dosage used varies: atoxyl, one to seven and a half grains (0.065 to 0.5 gm.), one to four times a week; soamin, two to ten grains (0.12 to 0.6 gm.); sodium cacodylate, three to seven and a half grains (0.2 to 0.5 gm.). Salvarsan has been extensively tried and variously reported as "a specific," "worthless," and "harmful." It is used in doses of from 0.1 to 0.6 gm. One should be on the watch for toxic effects especially if large doses of these preparations are used. The arsenite of iron, hypodermically administered, is of great value, especially if anemia is marked. Strychnine and ergotin are recommended when physical and mental depression are present. Hexamethylenamine and thyroid extract have been used with doubtful results.

For the nervous symptoms, notably insomnia, nothing is as valuable as hydrotherapy; this is often unavailable and drugs must be used. Veronal, trional, sulphonal, bromides, paraldehyde, chloral, opium, and perhaps hyoscine, may be tried.

Treatment of the *stomatitis* usually avails little, though solutions of silver salts may be of service. Atropine may lessen the flow of saliva. Mouth cleanliness is essential. For the vomiting, veronal, chloretone, soda, ice internally or applied over the epigastrium may be tried; morphine may be necessary but may prove useless. The diarrhœa is frequently very resistant and even opium, usually required in severe cases, may be of little value. Cold to the abdomen sometimes quiets peristalsis; bismuth, tannigen, and other astringents are of some value. In some cases dilute hydrochloric acid in large doses has a marked effect.

The *erythema* should be treated as a sunburn. If the skin is unbroken, nothing is required but protection from the sun's rays, with, perhaps, a cooling application such as calamine lotion. If there are raw surfaces, a 10 per cent. boric acid ointment may be applied to prevent infection; if this occurs, appropriate measures are to be instituted.

Cole and Winthrop have directed attention to the *transfusion* of blood in pellagra. No specific effect follows this operation, but occasionally such an acquisition of healthy blood may help a pellagrin through a crisis.

Complications should be treated with appropriate remedies and the stools should be examined for parasites and ova.

In caring for a pellagrin one should be ever mindful of the fact that the serious effects of the pellagra poison, be what it may, are upon the nervous system.

CHAPTER XIV

BERIBERI (KAKKE)

By MAXIMILIAN HERZOG, M.D., LL.D.

Definition.—Beriberi—polyneuritis endemica (Baelz), neuritis multiplex endemica (Scheube)—may be defined as an acute, subacute, or chronic disease, which is characterized clinically by disturbances of the circulation, of motion and of sensation, and associated anatomically with hypertrophy and degeneration of the heart and degeneration of the peripheral nerves and of the voluntary muscles. Attention may be called primarily to the fact that clinically the disease varies considerably and that its etiology is still very incompletely understood. Hence, it is really almost impossible to give a concise, satisfactory definition of the disease, although the affection is undoubtedly an entity, and can be diagnosed as a rule without much difficulty. In Japan, which is the country where the disease is, or at least formerly was, most prevalent, and where it has been studied most extensively, both clinically and pathologically, the malady is known as Kakke.¹

Geographical Distribution and Racial Predisposition.—The disease is generally prevalent in tropical and subtropical countries, where the humidity is, as a rule, considerable. It is found in Asia—in Japan, including Formosa, in China, the Malay Archipelago and Peninsula, the Dutch possessions and in eastern India; it is also quite prevalent throughout the Philippine Islands. It occurs on the eastern coast of South America, particularly in Brazil, and a number of reports have come from Africa of its presence there during the last two decades. Some isolated epidemics have also occurred in England and Ireland, and sporadic imported cases have been encountered in Continental Europe, the United States, and Canada.

Certain races are particularly susceptible to the disease, and wherever they travel are liable to disseminate it. This has been observed especially in the Japanese, the Chinese, and the Malays. The great prevalence of the disease in Japan has been emphasized by all writers on the subject. Baelz and K. Miura² in an article on beriberi, state that probably 50,000 cases of beriberi occur each year in Japan. These figures, however, are much too low for the period of the late Russo-Japanese war, because

¹ The disease is known by a variety of names in different countries where it is prevalent. For further information on the terminology and on the real or supposed etymology, the reader is referred to Scheube, *Die Beriberi-Krankheit*, Jena, 1894; and Scheube, *Die Krankheiten der warmen Länder*, 4th ed., Jena, 1910. An almost complete list of the very extensive literature of the subject will also be found there.

² Baelz and K. Miura, "Beriberi oder Kakke," *Mense's Handbuch der Tropenkrankheiten*, Leipzig, 1905, ii, p. 140

during 1904, from February to December, more than 50,000 Japanese soldiers sick with beriberi were brought back from the field to the home country, while in the Japanese army at home for the same period of time several thousand cases more developed. These figures, it is to be understood, do not include any cases which occurred outside of the army among the general population. In the Philippine Islands 3334 deaths from beriberi were reported in 1910.

Etiology.—This is far from being definitely and satisfactorily understood. Wright,¹ in giving a summary of the theories regarding the etiology of the disease, mentions the following: (1) Gelbke's theory that beriberi is due to dry fish infected with a trichina; (2) M. Miura's theory that it is due to the ingestion of certain kinds of raw fish, principally cambride, (3) Grimm's theory that it is due to the ingestion of infected fish; (4) Takaki's theory that it is due to a pathogenic diet in which nitrogen is deficient; (5) Ross' theory that it is due to arsenic poisoning; (6) the theory that it is due to the ingestion of mouldy rice; (7) Braddon's theory that it is due to the ingestion of a specific organism which develops on growing rice; (8) Manson's theory that it is due to a place germ (earth, floor or house) which distils a toxin, volatile or otherwise, that, being inhaled or ingested, produces the disease; and (9) Glogner's theory that it is due to a plasmodium. Other theories as to the etiology are that it is an anemia of a pernicious type, that it is a modified and secondarily changed form of scorbutus, that it is due to carbon monoxide poisoning, that it is caused by *Anklyostomum duodenale* or by *Trichocephalus dispar*. A number of investigators have laid claim to the discovery of a specific microorganism:

Not a single one of these hypotheses is tenable and some of them even lack the very semblance of any support. Many cases of beriberi occur in well-nourished strong individuals, and the blood examination in acute or recent cases shows neither pernicious anemia nor any anemia at all. The author has examined the blood in a number of acute and chronic cases and has found no characteristic blood changes, although the cases of longer standing may show a varying degree of secondary anemia.

Several investigators during the last few years again have attempted to solve the problem of the etiology, and while Scheube in the last edition of his book on *Diseases of Warm Countries* (Jena, 1910) again reaffirms his former view that beriberi is an infectious disease, a number of authors strongly hold that the malady is due to the lack in the food of a necessary constituent. The latter is claimed to be present sufficiently in unpolished rice, but insufficiently in polished rice. However, authors are not at all agreed upon the nature of this beriberi (neuritis) preventing agent present as alleged in unpolished rice. Shiga holds that the disease appears where there is a deficiency of a certain substance in the food and that it may indirectly be brought about by all conditions which cause a loss of nutrition. The preventive substance Shiga holds is contained in rice bran, is soluble in alcohol, and can be separated from the other ingredients which have no curative value. Strong and Cromwell from experiments

¹ *An Inquiry, etc., into Beriberi*, Singapore, Kelly and Walsh, May, 1902.

made upon prisoners in the Manila Penitentiary come to the conclusion that the disease is certainly not infectious in nature, but that it develops owing to the absence of some substance or substances in the diet necessary for the normal processes of the body; this substance is present in unpolished rice and rice polishings, but absent in polished rice. Fraser and Stanton hold that the beriberi preventing substance in unpolished rice is phosphorus pentoxide, present in the former to an extent of about 0.53 per cent. and reduced in polished rice to 0.26 per cent. Vedder likewise believes that the neuritis (beriberi) preventing substance is contained in unpolished rice. He is of the opinion that this unknown substance is an organic base as first claimed by Funk.

The most recent claim to the discovery of a specific germ, a diplococcus, for beriberi was made by Okata and Kokubo, two Japanese army surgeons, who have had an excellent opportunity to study the most extensive beriberi material among the Japanese soldiers transferred from Manchuria to Japan during the recent Russo-Japanese war. The author, working in the Hiroshima Kakke Hospital under the direction of Surgeon-Major Kokubo, had an opportunity to isolate these organisms from cases of beriberi in Hiroshima. A study of the cultures, as well as of those isolated by Kokubo and Okata, by no means convinced him of the specificity of these organisms. The author¹ has besides failed to obtain the same coccus from typical cases of beriberi in the Philippine Islands, and inoculation experiments on monkeys with the *Kokubo-Okata kakke coccus* have been absolutely negative. In about fifty cases of beriberi occurring in Manila, blood cultures failed to demonstrate any specific beriberi microbe. Koch, who had previously examined the blood of beriberi patients by this method, likewise had negative results.

The etiology of beriberi was extensively discussed at the International Medical Congress at London, 1913. Funk has reaffirmed his *vitamine* theory. His latest experiments, he claims, show that the beriberi preventing, eventually beriberi curing substance, which he calls *vitamine*, is soluble in water, alcohol and acid alcohol, is not dializable, and is destroyed at a temperature of 130° C. Shibayama holds that beriberi is not a phosphorus starvation and Zuzuki, another Japanese worker, calls the hypothetical beriberi-preventing substance *aberlic acid*. On the whole the majority of the Japanese investigators seem to believe that beriberi is due to an intoxication by a poison which is produced by an unknown microorganism in the human body, especially in the intestinal tract.

Larger outbreaks of beriberi are generally observed where there is a crowding together of many individuals into a limited space, as in prisons, barracks, asylums, schools, vessels, etc. Hence, beriberi frequently has the character of an institutional disease. The climatic conditions most favorable to the development of the disease are moisture and heat. It is most prevalent, as stated above, in tropical and subtropical countries. In countries where beriberi occurs, it is usually found in the lowlands near the sea or in alluvial territories along great rivers.

¹ *The Philippine Journal of Science*, 1906, vol. i, No. 2; "Studies in Beriberi," *Ibid.*, No. 7, 1906.

It is, as a rule, not found in the higher altitudes, although occasionally it does gain a foothold in mountainous regions. The disease is much more common in the male than in the female sex. However, attention should be called to the fact that pregnant women seem to be particularly liable to acquire it.

It most commonly occurs between the ages of fifteen and thirty years. There is certainly no doubt that some races, such as the Japanese, the Chinese, and the Malay, are particularly prone to contract the disease. Americans and Europeans are generally not very susceptible even when living among the natives where the disease is prevalent. However, their immunity is by no means absolute. The author has seen a few cases of beriberi among Americans in the Philippine Islands, some of which terminated fatally.

Polyneuritis in Birds.—Eykmann in 1889 in Batavia noticed that chickens suffer from a polyneuritis. Braddon and others confirmed and extended these observations and numerous investigators have studied this polyneuritis in chickens and pigeons. It was found that the disease occurred spontaneously when domestic fowl were fed on spoiled, mouldy rice, and the exclusive feeding of shelled boiled rice frequently produced a polyneuritis in these birds. A number of authors have held that polyneuritis of fowls is identical with beriberi in man and have tried to solve the mystery of the etiology of beriberi in man by a study of polyneuritis of fowl. However, the preponderance of evidence seems to be against the theory of such an identity. This is also the latest view of Shibayama, who says that the study of the beriberi-like disease in birds has but little to do with the recognition of the causative agent of human beriberi. The present author is likewise of the opinion that it has not been proved that polyneuritis in birds is identical with beriberi in man, on the contrary, this does not seem to be very probable. Attention should be called to the fact that there is a polyneuritis of roosters with disturbances of locomotion and final paralyses which certainly is not identical with beriberi and polyneuritis occurs in other domestic animals independently of deficiencies in feeding or of such intoxications as arsenic or mercury poisoning.

Special Pathology.—In bodies of patients dead of beriberi marked postmortem rigor generally promptly develops. However, in cases which succumb slowly to the atrophic type or in which complicating wasting diseases, such as tuberculosis, amœbic dysentery, etc., are present, the postmortem rigidity may be quite insignificant; this, however, is the exception and not the rule. The skin is pale, with cyanotic patches here and there, and occasionally cutaneous hemorrhages.

On section, the superficial veins discharge a large amount of dark fluid blood, and in the majority of cases, excepting only those of the atrophic form of long standing, the subcutaneous tissue is œdematous. The subcutaneous œdema is usually best marked in the anterior thoracic region and over the anterior surfaces of the lower extremities. Hydropericardium, ascites, and hydrothorax are very frequently encountered, hydropericardium being the most common. Subepicardial and subpleural petechiæ are also not infrequently encountered. Of the internal organs,

the heart shows characteristic changes most constantly. The myocardium, as a whole, is hypertrophied; this is usually most marked in the right ventricle, but the left may likewise be enlarged. The organ then is increased in all its diameters and in its weight. The right ventricle in particular is generally not only hypertrophied, but also markedly dilated, so that a relative insufficiency of the tricuspid valve is present. All of the chambers generally contain a large amount of dark fluid blood. The coronary veins are much dilated. The myocardium may be normal but quite frequently it is found to be more or less cloudy and mottled in consequence of diffuse fatty degeneration. The lungs are, as a rule, œdematous, congested, and contain little air; however, occasionally they are emphysematous, and sometimes collapsed and dry. Occasionally some catarrhal bronchitis is seen, and, when the pneumogastric has been profoundly affected, aspiration pneumonia has been observed.

The spleen shows no characteristic changes. However, this organ frequently exhibits cyanotic induration of a moderate degree. The kidneys in acute cases are markedly congested, and moderate cloudy swelling and fatty degeneration are occasionally observed. The liver is generally somewhat swollen and congested. Where chronic passive congestion has existed for some time, there is the characteristic appearance of the nutmeg liver. In many cases, particularly of the subacute variety, which have not existed for a very long period, we find great hyperemia of the gastric and duodenal mucosa and occasionally ecchymoses. In some cases blood clots are present in the stomach, possibly due to persistent vomiting prior to death. This condition of the gastric and duodenal mucosa has so impressed several observers that they maintain the stomach and duodenum to be the portal of entrance of the specific virus of beriberi. The small intestine, excepting the duodenum, and the large intestine show no particular changes.

The peripheral nerves, particularly those of the lower extremities, are almost without exception profoundly affected, but the changes are rarely noticeable to the naked eye. The lesions clearly indicate that the most characteristic anatomical morbid process is the degeneration of the peripheral nerves. The microscopic changes are a degeneration of the myelin sheath and of the axis-cylinder. The former breaks up into roundish or irregular fragments, which are arranged more or less like a row of beads. Later the myelin sheath may also show a honey-combed or foamy condition, or it may disappear entirely over longer distances of the nerve fibre. When such is the case, the axis-cylinder likewise gives evidence of degeneration. It is irregularly twisted and retracted and finally also entirely disappears so that nothing is left but an empty collapsed neurilemma. The nuclei of the latter are increased, but there is nowhere any sign of an active inflammatory process, although there may be a moderate number of leukocytes, evidently phagocytes, which enclose material from the degenerating myelin substance. The muscles supplied by such nerves likewise show degenerative processes. These manifest themselves first by a loss of striation. Where the process is more advanced, the sarcoplasm is changed into irregular hyaline masses; the fibre, as a whole, is shrunken, and between these masses

clefts and spaces are seen, which, during life, were filled with an œdematous exudate.

Yamagiwa¹ enumerates the following as the most important pathological changes: (1) Dilatation and hypertrophy of the right ventricle, and dilatation of the left; fatty metamorphosis of the myocardium; (2) degeneration of the peripheral nerves; (3) atrophy and degeneration of

the skeletal muscles; (4) parenchymatous degeneration of the kidneys; (5) hydrops. The pathological changes are regressive in nature, with the single exception of the hypertrophy of the myocardium.

Varieties and Symptoms.—From a clinical standpoint, beriberi may be divided into three chief forms: namely, acute pernicious, wet or œdematous, and dry or atrophic beriberi. This classification is, however, somewhat arbitrary. Besides the three well-defined forms, a rudimentary variety occurs quite frequently, in which the symptoms are so mild that medical aid is generally not sought. In these cases there is generally noticed a certain malaise, weakness of the lower extremities, and increased heart-beat on slight exertion. These symptoms may speedily disappear spontaneously, or increase in intensity and lead to one of the severer forms of the disease.

In the acute pernicious form, the onset is generally quite rapid. The patient becomes ill, apparently without premonitory symptoms. A feeling of oppression develops in the chest, dyspnœa, forced respiration, evidences of great venous congestion, frequently vomiting and the signs of rapid heart failure appear and death supervenes. Both the œdematous and the atrophic types generally develop in the same manner. Preceding the actual outbreak, there is a period of malaise, during which dull pain in the stomach, lack of appetite, and heaviness in the lower extremities and occasionally in the upper ones are complained of. One of the earliest

symptoms usually referred to by the patient is palpitation of the heart on slight exertion; next, pain in the legs is frequently noticed, particularly in the calves, which soon become tender on pressure. Later the gait becomes unsteady; the patient walks as if it were difficult, as indeed it is, to lift the feet from the ground. The gait of a person sick

FIG. 48



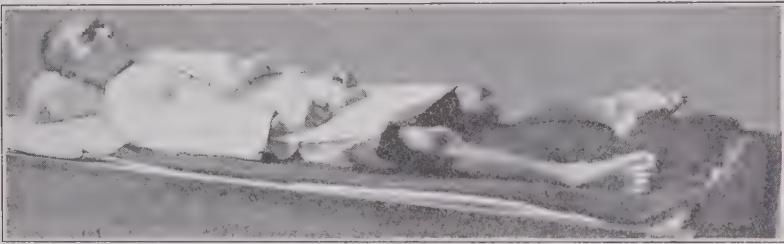
Wet beriberi, showing œdema of the legs and feet. (Author.)

¹ Yamagiwa, "Beiträge zur Kenntniss der Kakke," *Vir. Arch.*, 1899, clvi, p. 451.

with beriberi has not been improperly compared to that of a man walking in soft and very sticky clay, or to that of a man, heavily dressed, who has been in the water and whose clothing is heavy from the fluid absorbed. At this stage, in the case of the *wet* form, an œdema of the lower extremities is generally noticeable. It is particularly well marked over the anterior tibial region, over the dorsum of the feet and around the ankles. Here the skin pits on pressure. In the *dry* form, a slight œdema may be present at an early period, but this is not well marked and is transitory. The lower extremities in this variety, instead of being swollen, progressively become more and more emaciated and the muscles become atrophic, often indurated, and contracted. Together with the disturbances of locomotion, disturbances of sensation develop simultaneously.

Hypesthesia of the lower extremities is the most common form of disturbance of sensation. This generally begins on the anterior or external surface of the legs and frequently extends to the dorsum of the feet and toes. It is found in the territory supplied by the peroneal and saphenous nerves. Accompanying hypesthesia, there is a subjective

FIG. 49



Dry beriberi with great atrophy of the muscles of the legs and equinovarus position of the feet. (Author.)

paresthesia. If the skin is touched with a soft camel's hair brush, the patient feels as if paper intervened between the skin and the brush. The intensity and the extent of such disturbances of sensation vary not only in different individuals but also at different times in the same individual. These disturbances have a tendency to spread upward from the feet and legs. In the severer cases the upper extremities are similarly affected. The face is rarely involved, but occasionally disturbances of sensation are found around the mouth. True anesthesia is rare, as is also hyperesthesia. The disturbances of motility generally begin as a sensation of weakness in the legs, which is first noticed in the calves and later on in the thighs. After these have lasted for some time, atrophy is generally evident or it may appear even before distinct paralysis becomes obvious. Usually the anterior sharp edge of the tibia becomes more prominent, the calf becomes thin and flabby and the thigh gradually becomes emaciated. When more or less contraction is associated with the atrophy, the foot assumes an equinovarus position. In severe attacks, similar changes occur in the upper extremities. Paralysis of the lower extremities is much more common than paralysis of the upper

ones; but in the severest cases both feet and hands, including the toes and fingers, may be paralyzed. The hands and fingers in such cases may occasionally be more affected than the feet. In the gravest types neither the hands nor the fingers can be flexed toward the dorsum, and there is complete wrist-drop.

The electrical excitability shows various degrees of change, from a simple diminution to a complete reaction of degeneration. According to K. Miura, one can foretell from the position of the foot and toes the result of the electrical tests. If the foot can be moved easily on the ankle-joint, one finds only a diminution of electrical excitability. If the toes, but not the foot, can be flexed dorsally, we encounter only a partial degeneration reaction. If, however, neither the foot nor the toes can be moved voluntarily, we then have a complete degeneration reaction. Paralysis of the diaphragm and of the intercostal muscles occurs only in the severest cases. In addition to the nerves of the extremities, other nerves are also more or less frequently involved. Paresis of the muscles of the larynx is by no means rare; in fact, it is a very common occurrence to find hoarseness and more or less complete aphonia. Paresis of the facial nerves and of the nervus abducens has occasionally been observed, as also have been disturbances of the optic nerves, manifested by central scotoma, and in rare cases by amblyopia. Among the late symptoms, which at this time become frequently quite prominent, are contractions of the muscles, particularly of the gastrocnemius.

If an early examination be made, both in the hypertrophic form and in the atrophic dry one, the following symptomatology may be found; the pulse is generally rapid, somewhat irregular, rather weak, and easily compressible. On slight exertion, sometimes even so slight as sitting up in bed, the rate increases 20 or 30 beats a minute. The apex of the heart, sometimes quite early and frequently later after the disease has existed for several days, is found displaced upwardly and outwardly and the area of visible impulse is enlarged. The area of heart dullness is increased to the right. Where there is hypertrophy of the left ventricle, the area of dullness is also increased to the left. At the apex some change in the first sound may be found; but the most common sign is generally a marked accentuation of the second pulmonic sound. Sometimes a definite systolic bruit may be heard at the apex. Frequently there is a reduplication of the second sound both at the apex and in the pulmonic area. In a considerable number, as was first prominently pointed out by M. Miura, a musical sound is heard over the crural arteries, which may be audible even at a distance of several feet from the patient.

In the early stages, sometimes up to the sixth or seventh day, the patellar reflex is increased. Then a diminution of the knee-jerks appears, and finally they are entirely absent. Even in cases which terminate favorably the absence of the knee-jerks may last a long time and may be present after the disturbances of locomotion have disappeared. When the knee-jerk begins to reappear, it generally again becomes temporarily accentuated, and then finally returns to the normal. It has already been mentioned that the muscles of the calves of the leg are frequently painful

and very tender to pressure. The skin, particularly of the lower extremities, shows disturbances of sensation. There is general hypesthesia or paresthesia, and less frequently complete anesthesia.

In mild cases the urine is somewhat decreased in amount, and in severe ones considerably so. The diminution is sometimes very great, and the daily amount may fall below 100 cc. The specific gravity in such cases is increased, but not proportionately to the great diminution in amount. Albumin is generally not found. When, however, it is present, only traces occur. However sometimes, though rarely, a complicating nephritis develops in the later stages, and then albumin is constantly present. Indican is very frequently found in the acute and œdematous varieties.

According to most authors, the temperature in uncomplicated cases is either normal or very slightly elevated. When a marked rise of temperature is met with, it is usually owing to some complication. In all cases seen by the writer in which there was a marked rise in temperature during life, at autopsy some complicating lesion was found.

In cases either of the œdematous or the atrophic form which progress unfavorably, the dyspnœa and the difficult respirations increase and the resulting grave circulatory disturbances find their expression in a superficial venous congestion, with visible throbbing veins. While consciousness is preserved, the dyspnœa and the suffering increase, and the face of the patient presents a picture of grave anxiety, such as may be seen in angina pectoris. Death frequently occurs quickly in consequence of heart failure. Stanley¹ has drawn attention to the frequency of *sudden heart failure* in diphtheria and in beriberi. His analysis of 340 cases of the latter disease shows 72 fatal instances, of which 31 died of rapid heart failure. The pulse tension was lowered in 254 cases, and dilatation of the heart existed in 98. The second sound was reduplicated in 245, and the first in 35. There were cardiac murmurs in 84. When the disease ends in recovery, the disturbances of circulation decrease in intensity. In the wet form there occurs a profuse secretion of urine and the œdema gradually disappears. In both types which progress favorably, the disturbances of sensation and the paralyses disappear gradually and the patient regains the use of his limbs.

Beriberi occurring in infants fed by mothers sick with the disease has been described by Hirota. In these the disease generally presents the symptoms of the acute pernicious type, namely, restlessness, vomiting, dyspnœa, aphonia, rapid pulse, extension of the heart dulness toward the right, œdema, a musical sound over the crural artery, and absence of fever. When the child is taken away from the sick mother early, the symptoms generally disappear within two weeks. Andrews has studied beriberi in infants in the Philippine Islands. He holds that the high infantile mortality in this archipelago is largely due to beriberi caused by the lack of something (he calls it in a non-committal manner Vitamine) in the mother's milk. Andrews thinks that beriberi is neither an infection nor a toxemia, but a malady due to dietetic causes.

¹ *British Medical Journal*, 1903, ii, 1636.

Complications and Sequelæ.—The most common diseases associated with beriberi are tuberculosis and dysentery. When these coexist the prognosis is usually very grave. While most cases of beriberi end in rapid recovery, some have a protracted course and general weakness with or without anemia, difficulty in the use of the lower extremities, contraction and induration of the muscles of the calf, and also disturbances of motility in the upper extremities with diminution and disturbance in the quality of the sensation; palpitation of the heart and rapid pulse may remain for a long time. As a rule, these symptoms all disappear under proper treatment and diet. It has been noticed in Europeans or Americans who have suffered from severe attacks of beriberi and who have returned during convalescence to their native country, that the disease has generally a protracted course, from which recovery is very slow.

Diagnosis.—In many cases among the uneducated and ignorant Asiatics the diagnosis must be made exclusively from the objective symptoms, as an intelligible history is unobtainable. The most important points are the condition of the pulse while the patient is at rest and before he has been disturbed, and after he has been subjected to some physical exertion. If the patient is not too ill, he should be made to leave his bed and walk up and down the room a few times. While doing so the gait should be noted in order to ascertain whether it presents the characteristic appearance already mentioned. The pulse is then to be counted again. In beriberi it is usually accelerated and the rapidity increases very markedly on slight exertion. The percussion and auscultation of the heart are also of value. Particular importance attaches to the enlargement of the right ventricle, to the accentuation of the second pulmonic sound and to a reduplication of the second sound. The frequency of hydropericardium, hydrothorax, and ascites are valuable points, as also the increase of the patellar reflex in the early stages and the loss of it in the more advanced ones. The frequency of pain in the muscles of the calf, and of œdema in the leg and foot, has already been noted. The great decrease or even the suppression of the urine in the early stages of the œdematous form is also an important factor. The disturbances of sensation and of locomotion and the paralyses and contractions have been emphasized.

Among the diseases which might be confounded with beriberi are the following: *Myelitis* in which are present increased reflexes, ankle-clonus, paralysis of the extremities without muscular atrophy, paralysis of the bladder and rectum, complete anesthesia without pain in the muscles of the calf, no reaction of degeneration and no symptoms on the part of the heart and kidneys. In *Landry's paralysis* there is fever at the onset, and pain in the head, with much perspiration at the back and extremities. A study of the sensation and circulation reveals nothing abnormal. *Tubes* should not be confounded with beriberi or *vice versa*. In *anesthetic leprosy* a thickening of the peripheral nerves and a true anesthesia is found and not hypesthesia, which is generally encountered in beriberi. In addition, in leprosy, spots or nodules or diffuse thickening of the skin are usually encountered. A careful search will reveal the presence of

the lepra bacillus. Certain cases of *peripheral neuritis*, depending upon chronic alcohol or arsenic intoxication, may at times be exceedingly difficult to differentiate from beriberi. In Europeans and Americans living in tropical countries where beriberi is prevalent, and presenting symptoms suggesting this disease, *alcoholic neuritis* should first be excluded definitely before a diagnosis of beriberi is made.

Prognosis.—This varies greatly in different epidemics and in different localities. It is perhaps most fatal (an observation commonly made as to infectious diseases) when it first invades a new territory in which it has never been prevalent before. A very interesting account of what appears to have been the first outbreak of beriberi in the Philippine Islands has been published by Koeniger.¹ This author reports that when the disease first broke out in Manila, in 1882, the mortality in the first few months was not less than 60 per cent. Among Chinese in Sumatra and Java, epidemics with an equally high mortality have been observed. Stanley gives a mortality of 20 per cent. among the Chinese prisoners at Shanghai. Among the Chinese patients of the Hong Kong Government Hospitals during the last ten years, the mortality has been 50 per cent.² The death-rate in cases developing in Bilibid Prison at Manila is likewise quite high.³ These instances, however, represent somewhat exceptional and particularly unfavorable conditions. Under favorable conditions, the mortality is usually low. In Dutch India among the troops, the death-rate is given as between 2 and 6 per cent. Among the English East Indian troops the figures are somewhat higher. Scheube gives an average mortality of 3.5 per cent. for Japan. During the first year (1904) of the late Russo-Japanese war there were sent back from the front to the Military Reserve Hospitals of Hiroshima, Tokyo, etc., 50,340 Japanese soldiers sick with beriberi. Of these, 1024, or less than 2 per cent., died. During the same period of time there developed among the troops in Japan 3337 cases, of which only 44 died. So, on the whole, taking a very large material as a basis, the prognosis is quite favorable.

No definite prognosis can be made in an individual case, because a fatal termination from heart failure may occur at almost any stage during the course. Unfavorable symptoms are marked dilatation of the heart, great weakness and irregularity of the pulse and other grave disturbances of circulation, circumscribed œdema on the trunk, signs of œdema in the lungs, and particularly persistent vomiting. The last symptom is almost invariably the precursor of a rapid fatal termination in consequence of heart failure. The mortality in the acute pernicious form is always high; that in the subacute or chronic, œdematous type is lower but higher than in the dry atrophic variety. A favorable sign is the appearance of a copious renal secretion after partial or complete suppression of urine. Acute pernicious cases when

¹ *Deut. Arch. f. klin. Med.*, 1884, xxxv, p. 419

² Personal communication from Dr. M. V. Koch, Physician in charge of the Government Civil Hospital for Infectious Diseases.

³ Bilibid prison in Manila contains from 3500 to 4500 prisoners, and the hygienic conditions, under the circumstances, formerly were necessarily not the very best.

fatal always terminate by heart failure or asphyxia; in chronic cases death results from paralysis of the respiratory muscles, occasionally from aspiration pneumonia or by general debility. The latter event is particularly liable to take place when tuberculosis or amœbic dysentery is present. The average duration of acute pernicious beriberi is very short, while that of cases of moderate intensity and of moderately chronic character is perhaps between three and six weeks. Besides these there are a large number of protracted cases, which extend over a period of months and sometimes may last more than a year. These very chronic cases are characterized by muscular atrophies and joint fixation. But generally even these patients, if properly treated, and if placed under proper hygienic conditions, proper nutrition, etc., finally become completely well.

It has been, however, frequently noticed in Japan, the Malay Peninsula, and the Philippine Islands, that if a patient has had one attack, although he recovers completely, when exposed to the same conditions he suffers a second or even a third one.

Prophylaxis.—This is still in a decidedly unsatisfactory state. The observance of the ordinary rules of hygiene and sanitation has frequently shown a favorable influence in restricting the disease. However, in other instances, beriberi will become prevalent in certain localities and under certain conditions, in spite of all hygienic and sanitary measures. The late Russo-Japanese war furnishes a confirmatory example of this statement. The hygienic measures adopted in the Japanese army proved sufficient to limit to a minimum such diseases as typhoid, typhus, dysentery, scorbutus, etc., but they were of no avail against beriberi. There is one factor which beyond all doubt favors the occurrence and spreading of beriberi in those countries and among those races where it is at all prevalent, that is, the crowding together of large numbers of persons into limited spaces, as prisons, barracks, schools, factories, mines and ships. If beriberi appears under such environments, these places should, if possible, be abandoned as dwellings, at least, the number of inmates should be decreased, and a thorough disinfection, airing, and drying should be undertaken. Since recent observations and experiments have strongly pointed to a more exclusive polished rice diet as a possible source of beriberi, such a diet should be avoided and the ingestion of unpolished rice should be favored. Women sick with beriberi should not nurse children.

Treatment.—There is no specific treatment. The patient should be confined to bed. Even if he is suffering from what appears to be only a mild attack, nevertheless rest, in the beginning, should be insisted upon, since it is important to reduce the heart's action as much as possible in order to guard against future and often unexpected grave cardiac complications. It has generally been found very advantageous to administer the saline laxatives, such as magnesium sulphate, in large doses during the first stages of beriberi. This is given for five to seven days, followed by an intermission of a few days, after which the treatment is repeated. Other drugs recommended are cream of tartar, infusion of senna, Carlsbad salts, oleum ricini, and aloes and

jalap in the form of pills. Where there is marked œdema, Baelz and K. Miura recommend potassium acetate (90 gr., 6 gm.), potassium nitrate (30 gr., 2 gm.), or diuretin (45 to 60 gr., 3 to 4 gm.) per day. Scheube has strongly recommended the use of digitalis, but most observers consider it of very doubtful value, and it has been repeatedly stated that in many cases it has a decidedly injurious effect in that it tends to produce anorexia, nausea, and vomiting. In severe acute cases with great weakness of the heart, Baelz frequently observed good effects from large doses of cocaine given internally in amounts of from 1 to 3 grains (0.05 to 0.20 gm.) per day. In acute or subacute cases, with signs of dilatation of the right heart, while the pulse is still good, encouraging results have been obtained by bleeding, to the amount of several hundred cubic centimeters. However, when the pulse has become weak, this is dangerous, on account of the possibility of sudden heart failure. With dilatation, venous congestion and a weakened pulse, the withdrawal of blood by cups or leeches, applied over the precordial region, is often followed by improvement. The author has seen a considerable number of Japanese soldiers sick with beriberi who were greatly helped by this. However, the improvement is frequently only temporary and a repetition of the procedure may or may not bring about good results, or the unfavorable symptoms may increase in severity in spite of a temporary amelioration.

The diet should be light and nutritious and include considerable milk. Both in Japan and in Java beriberi patients frequently receive as a part of their daily nourishment the Adzucki bean (*Phaseolus radiatus*), which, it is believed, has both a favorable prophylactic and a curative tendency. In the Philippines similar virtues are claimed for the Mongo or Mungo bean (*Phaseolus Mungo* L.). Katjangidgo beans are recommended by Hulshoff Pol. Very favorable results in the treatment of beriberi have recently been reported by Thompson and Simpson by the internal administration of ordinary brewers' yeast. The latter is given in 1 dram doses, wrapped up in rice paper; one ounce daily. Rice should, in private practice at least, be withdrawn from the diet. This measure is necessary, not so much on account of its real value, as on account of the fact that there is still a widespread popular belief, in many regions where beriberi prevails, that a kakke patient should not eat rice. Hence, a physician who fails to remove rice from the daily dietary is liable at once to lose the confidence of his patient. A person sick with a severe type of beriberi, accompanied by grave circulatory disturbances, should not under ordinary conditions be moved to a distance. Even during the early stages of recovery, a long railroad journey may bring on a relapse with severe and dangerous heart symptoms. But cases mild from the onset, and serious ones after recovery, may with advantage be removed from a beriberi-infected neighborhood to a high and dry locality free from this disease. If there is a marked hyperesthesia (which, however, is rare in beriberi), bromide of potassium or morphine internally or chloroform externally are recommended. Vomiting and dyspnoea are frequently greatly ameliorated by small doses of morphine hypodermically.

It is very important that the muscular atrophies and contractions should receive early and proper treatment. However, it is not advisable to begin this as long as there is marked œdema of the affected extremities. When the œdema has subsided, massage and passive movements are to be practised systematically several times a day. As soon as the patient is able to do so, and when there is no longer any immediate danger of cardiac failure, moderate active exercise should be cautiously begun. Should such exercise lead to a very marked increase in the pulse-rate, it should be postponed. The atrophic muscles are to receive electrical treatment. When they still react to the faradic current, the latter is to be used. Where there is complete degeneration reaction, the galvanic current should be employed, with the cathode situated peripherally over the nerve and the anode centrally applied. In the use of the faradic current, Scheube recommends large sponge or roller electrodes, to be employed in a massaging manner. When there is paralysis of the phrenic nerve, M. Miura advises faradization, one sponge electrode being placed over the epigastric region and the other above and inside of the sternoclavicular articulation, or the two electrodes may both be placed on the sides of the neck.

For Europeans and Americans who have suffered from an attack of beriberi, a change of climate and return to a more bracing atmosphere should be recommended.

CHAPTER XV

AUTO-INTOXICATIONS

By ALONZO ENGLEBERT TAYLOR, M.D.

UNDER the term *intoxication* we understand a state of perversion of physiological function induced by the presence in the body of abnormal substances or by an excess or deficiency of normal metabolic constituents. Under the term *constituent* is understood not only materials of nutrition and metabolism, but also the physiological fluids and secretions associated with the different functions. It has been long apparent that the pharmacological definitions of intoxication are too narrow to comprehend the acts of morbid physiology; a definition from the point of view of general and experimental pathology must be made as broad as here stated. The mere presence of a known poisonous agent, the presence of an excess or the absence of the adequate amount of a normal substance, need not lead to any intoxication demonstrable under the circumstances of the occurrence or experiment; the reason for this lies in the singular adaptability of the metabolism and in the enormous toleration of the organism. To establish an intoxication there must be some disturbance in the function of the body. The definition must not be made so rigid as to exclude the morphological results of nutritional and metabolic abnormalities. We cannot afford to exclude from their bearings on intoxications the inflammations and degeneration produced in morphological structures by poisons, even at the risk of an apparently absurdly broad expansion of the term intoxication. A close consideration of the modes of action of poisons will justify this standpoint.

A general classification of endogenous intoxications, useful solely as a working scheme, is contained on page 504. Under auto-intoxications we group the intoxications of *endogenous* metabolic order. The systemic parasitic intoxications exhibit relations that are often very intimate. Indeed, it may be assumed that in the majority of infectious diseases a part of the deleterious result is due to auto-intoxications secondary to the metabolism of the bacteria. In some instances no other intoxications seem to be induced, and we may infer that some microorganisms are harmful solely through the excitation of an auto-intoxication. These auto-intoxications are of the nature of exaggerations of normal processes—katabolism, oxidation, and cytolysis.

Exaggerations of katabolism and oxidation are common in the infectious diseases. Individuals with infections may not be upon a metabolic balance; when no food is taken, the output is greater than a starvation output; and it often exceeds the input by more than a starvation output when the digestion is sufficient to maintain an ordinary balance. The patient wastes, owing to the excessive combustion of fat and muscle, and

the end-products of the excessive protein metabolism are found in the urine. It is in many instances possible to control this loss by high input of carbohydrate.

Endogenous Intoxications.	Parasitic.	<ul style="list-style-type: none"> Alimentary. Systemic. 	<ul style="list-style-type: none"> Due to bacterial processes. Due to higher parasites, as vermes.
		The infectious diseases.	
	Metabolic.	Oxidation.	<ul style="list-style-type: none"> Suboxidation. Superoxidation. Insufficiency of oxygen.
		Distoxication.	
		Overexertion.	
		Retention intoxications.	<ul style="list-style-type: none"> Retention of bile. Retention of perspiration. Retention of carbon dioxide. Retention of feces. Suppression of urine.
		Salts, acids, alkalis; acidosis.	
		Fever.	
		Infections.	
		Neoplasms.	
		Metabolism of protein.	<ul style="list-style-type: none"> Cystinuria. Alkaptonuria. Uremia.
		Metabolism of nuclein.	Gout. Oxaluria.
		Metabolism of carbohydrate.	<ul style="list-style-type: none"> Glycosuria. Diabetes.
		Metabolism of fats.	Acetone complex.
		Diseases of special organs.	<ul style="list-style-type: none"> Thyroid, adrenal, pituitary bodies. Pancreas, liver, etc.

An *acceleration of cytolysis* is commonly observed in infectious diseases. An excellent illustration is afforded by the red corpuscles. The life of the erythrocyte is limited. There is a regulatory mechanism whereby the formation of new cells is proportioned to the destruction of circulating cells; and there is a great reserve power of compensatory overproduction. A prolonged excessive destruction of red corpuscles, however, usually overtakes the centres of regeneration, and a reduction of the unit of circulating cells is the result. An acceleration of the normal rate of destruction of erythrocytes is a very common result of infectious diseases. It is usually not to be attributed to the specific poison. Some of the poisons, as the venoms, are directly erythrolytic and certain bacteria contain similarly active substances; but of the known and isolated toxins, few are erythrolytic, and the erythrolysis must be attributed to other than the principal product of the bacterial metabolism. In nephritis, carcinomatous cachexia, scarlatina, and in toluylene-diamine poisoning, for example, we have the same oligocythemia, resting upon an acceleration of the normal rate of destruction. Similar considerations hold for the glandular structures of the body, especially the liver and kidney. Such cytolytic degenerations are most common in infectious diseases. How these accelerations of cytolytes are brought about we do not know. The nearest suggestion is that the process is one allied to fermentation, and this is supported by chemical study and by the observation that autolysis is more rapid in diseased and degenerating than in healthy organs. Another suggestion is that there is a chemical combination between some poison and a protoplasmic or nuclear con-

stituent, resulting in the death of the cell. This has been made positive for certain cells by recent researches in experimental cytolysis, but we do not know to what extent it occurs in natural disease.

However produced, it is apparent that the functions of tissues must be disturbed by these cytolysees and an auto-intoxication might result. It is possible that the products of tissue degeneration may be in themselves toxic. Thus cholin is derived from the cleavage of lecithin, and investigations have suggested that possibly to this or allied substances may be attributed some of the symptoms observed in general paralysis and other degenerative diseases of the central nervous system. In tetanus, the specific toxin seems almost entirely to dominate the symptomatology and these additional processes are not observed; tetanus is almost as specific and localized an intoxication as strychnine poisoning. In sepsis, on the other hand, the exaggeration of katabolism and cytolysis is so marked as to suggest that in these directions lies the chief and specific intoxication. This is not the place for a discussion of the nature of the infectious processes, but, in connection with true metabolic auto-intoxications, these secondary auto-intoxications associated with infectious diseases demand a brief mention.

A separation of auto-intoxication from the general pathology of metabolism is not possible, since all alterations in general metabolism, if they lead to consequences, thereby become auto-intoxications. It is furthermore desirable from every point of view that the study of the auto-intoxications should be carried out from the point of view of and based upon the physiology of metabolism. We are all familiar with the conception of the chemistry of life as a series of processes building up to the cells and dismantling from them, assimilation up to the plane of biological dignity and dissimilation to the plane of simple products. The possibility of a misstep in the various stages of anabolism or katabolism would furnish the occasion for a perversion of function, an intoxication. It is upon these general considerations that the current views of auto-intoxication are based. The danger of this conception is that it disregards entirely two most prominent attributes: the power of adaptation to alteration in the media of existence; and the power of compensation, of carrying an overload. We have many illustrations of the depletion and overtaxation of certain organs and functions and of how admirably the body compensates for them. For every function it is known that a heavy overload may be well borne through a prolonged period. Under these circumstances it is absurd to say that we are all on the verge of an auto-intoxication; living, so to speak, over a charge of dynamite that may each instant be provoked to explosion. This view of auto-intoxication is an unwarranted use of a physiological concept. This conception of our metabolism, and its leeway of adaptation and compensation, is not only supported by our best chemical studies upon the subject, but is in harmony with the common-sense experience of mankind. It is to the use of this loose and subjective interpretation of the facts of metabolism and their relations to disease, that the term *auto-intoxication* has become the limbo into which untrained practitioners consign undiagnosed cases.

GASTRO-INTESTINAL AUTO-INTOXICATION

A discussion of gastro-intestinal auto-intoxication in the strict sense may, according to our present knowledge, be considered under five headings: Digestive fluids and secretions; normal products of digestion; abnormal products of digestion; substances formed normally from food by bacteria within the alimentary tract; and abnormal products of bacterial disintegration. It is clear that specific bacterial infections of the tract fall outside the term "auto-intoxication." How indigestions and dyspepsias (not dependent on abnormal food or bacterial processes) are to be classified is not yet apparent.

Intoxication by Resorption of the Digestive Juices.—The digestive juices have a certain toxicity independent of their salts and reaction. Pepsin, trypsin, and erepsin, when injected into the circulation, produce cellular degenerations, alterations in the corpuscles and coagulability of the blood. It is by some assumed that these ferments are resorbed in normal life and rendered harmless by some process of distoxication. This granted, it is natural to assume next that the postulated distoxication may become disturbed and an auto-intoxication result. That the intestinal tissue behind the lining epithelium contains ferments is an experimentally established fact. Beyond this there is not a single reported experimental fact, exact observation, or clinical fact that is explained by the assumption of the resorption and non-distoxication of the digestive juices. We have considerable experimental knowledge of the toxicity of pancreatic juice and of the secretion of an isolated loop of upper intestine. It is not clear that this knowledge has any meaning in relation to gastro-intestinal auto-intoxication.

The Products of Normal Digestion.—Some of these are toxic. The albumoses and peptones, on parenteral administration, produce symptoms of shock, in smaller doses often repeated, fever, leukocytosis, alterations in the coagulability of the blood, hemolysis, and cellular degenerations—all conditions not particularly associated with so-called gastro-intestinal auto-intoxication. In the severe degenerative diseases, as acute yellow atrophy of the liver, acute pancreatitis and septic exudations, these proteins may be found in the blood plasma. The writer is acquainted with no experimental work or clinical investigations tending to show that these lower proteins are responsible for any gastro-intestinal auto-intoxication. The experimental observations on so-called peptone shock have no apparent bearing upon alimentary auto-intoxication. Purified peptone is not poisonous.

The amino-acids are quite innocuous so far as they have been investigated. Amino-nitrogen is found in all organs and in the circulation. In conditions attended with excesses of cellular degeneration, as in acute yellow atrophy of the liver, large quantities of these substances have been found in the blood and the tissues. There are no reported analyses tending to show that, in connection with gastro-intestinal auto-intoxications, the content of amino-nitrogen in the blood or urine is increased.

The products of the digestion of fats must also be held guiltless. Glycerol is somewhat toxic; there is normally no glycerol in the urine. Since the fats are found resynthesized in the retroperitoneal lymph vessels, it is apparent that the glycerol split-off during the digestion has been again used in the recombination. The fatty acids themselves cannot be a factor, because, when administered, they are easily absorbed and converted into fats by the addition of glycerol. The products of the carbohydrate digestion are entirely innocuous.

Abnormal Products of Digestion.—Of qualitative variations in the digestion of protein we know little. In the complete hydrolysis of protein a large number of amino-acids are formed. Recent investigations indicate that the different proteins contain the same amino-acids but in different relative amounts and probably in different combinations within the molecule. It is conceivable that under abnormal conditions the products of digestion might suffer some alteration, either within the tract or during the process of absorption. We have no facts that indicate that such is the case. There is, in connection with the digestion of fats, one recognized possibility for an abnormal deviation—the formation of β -oxybutyric and diacetic acid. There is one group of cases of acetonuria associated with gastro-intestinal symptoms, but the keton substances are not formed in the alimentary tract. In connection with the digestion of carbohydrate, a gastro-intestinal oxaluria is theoretically possible, the oxalic acid being derived from glucose. Cystinuria and alkaptonuria were once regarded as of gastro-intestinal origin, but this point of view cannot now be maintained.

Substances Formed by Bacteria from Normal Food within the Alimentary Tract.—The normal digestive tract contains many saprophytes and not a few pathogenic bacteria. The temperature is favorable, nutrient media are abundant, the products of their metabolism are regularly removed, and we have the best evidence that fermentations and putrefactions are constantly in operation. The material consumed in these operations is not large; over nine-tenths of the food is absorbed in digestion and the larger portion of the remainder is residual in the feces. This is not due to the antiseptic properties of the digestive juices, but rather to the rapidity of the processes of digestion and absorption, and to the brief residence of the residue in the tract.

Do the products of the normal bacterial disintegration of normal food give rise to intoxications? Under conditions of increased virulency upon the part of the bacteria normally present, may not greater quantities of the normal products be generated, resulting in an intoxication? One must attempt to separate systemic intoxication from local irritation. The stools of children with acute enterocolitis may present the acidity of a tenth-normal acid, due to acetic and butyric acids. Now since the ammonia and fixed alkalis of the urine need not be increased in these cases, it is clear that the children are not suffering from an acid intoxication by absorption. But there can be no doubt that such a degree of acidity causes irritation and inflammation of the mucous membrane and might be responsible for colic, diarrhœa, and fever. The products of normal fermentation and putrefaction within the alimentary tract

are, so far as we know, the following: From the fermentation of carbohydrates are derived formic, acetic, butyric, propionic, valerianic, lactic, succinic, and traces of oxalic acids. Apart from oxalic acid, none of these are toxic beyond their acidity. The quantities formed are not large. They are in large part absorbed, since normal feces contain but traces of them. Their neutralization and oxidation entrains, in all probability, no metabolic difficulties, and we may regard them as innocuous. The same acids could in part, together with oxy-acids, be derived from the bacterial disintegration of the fats; this occurs but to a slight extent, since fatty acids are very difficult of fermentation. The putrefaction of protein yields the derivatives of the benzol nucleus—indol, skatol, phenol, and cresol; derivatives of amino-acids, hexone bases and their derivatives; sulphurous bodies, such as mercaptan, hydrogen disulphide, and other unclassified bodies containing neutral sulphur. Indol, skatol, phenol, and cresol are, in the quantities concerned, quite non-toxic. The amino-acids are quite harmless; they are absorbed and either elaborated or oxidized. The sulphur bodies are of unknown importance. Hydrogen disulphide is, of course, toxic, but the quantities concerned are trivial. Carbon dioxide, nitrogen, acetone, alcohol, methane, and other hydrocarbon gases that exist in traces, cannot be convicted of any toxic effects.

Thus the sum total of our present knowledge is that in the normal bacterial disintegration of foodstuffs in the alimentary tract no known toxic substance is formed. It is, of course, possible that even normal saprophytes evolve specific metabolic substances toxic to the host.

Are these bacterial processes sometimes so excessive as to cause a direct intoxication? In infantile enterocolitis the organic acids may be produced in excessive quantities and possibly these are responsible for some of the acid intoxications; we do not know whether these fatty acids cause acidosis or whether it is always due to the acids of the ketone group. Intoxication with hydrogen disulphide occurs certainly, though rarely. When so much hydrogen disulphide is absorbed as to appear unoxidized in the urine, it is proper to attribute to it the suggestive toxic symptoms that are present. Large quantities of lactic acid are sometimes found in the stomach; indeed, there are paroxysmal attacks accompanied by excessive formation of this acid.

In many conditions of the alimentary tract the benzol derivatives are increased in the urine. While this should be interpreted to mean nothing more than that the bacterial processes in the intestine are increased, it is usually interpreted as a sign of auto-intoxication. Indol and skatol are products of the action of bacteria on tryptophane. They are for the most part absorbed, eliminated, paired with sulphuric and to some extent with glycuronic acid, and in small part as oxyacids. Skatol-carboxylic acid is in part eliminated as a salt, in part oxidized. The phenol and cresol are derived from tyrosin. They are absorbed, in large part oxidized to hydrochinon and pyrocatechin (which pair with sulphuric acid); the rest is eliminated paired with sulphuric and glycuronic acid. Paraoxyphenyl-acetic and -propionic acids, intermediary products in the derivation of phenol from tyrosin, appear as salts in the urine,

but bear no constant relation to either the tyrosin or the phenol. Hippuric acid, apart from that obtained from the vegetable diet, is possibly derived from phenyl-alanine. Normally the absorption of these substances is very good, but this cannot be assumed and should be controlled by examination of the stools.

There is normally little putrefaction but much fermentation in the small intestine. Diarrhoea usually leads to a diminution of putrefaction, but in typhoid fever, dysentery, and intestinal tuberculosis we often observe an increase. There is no relation between gastric acidity and intestinal putrefaction. There is no constant relation between intestinal putrefaction and the biliary secretion. Intestinal putrefaction is dependent to some extent upon the diet. With an excess of protein, an abundant substrate is afforded the bacteria. In the qualitative sense the products of intestinal putrefaction may depend to some extent upon the particular proteins contained in the diet. Proteins that yield much tryptophane on hydrolysis will yield much indol, skatol, and their derivatives; proteins that yield much tyrosin on hydrolysis will yield much phenol and cresol and their derivatives. Thus serum albumin and globulin, fibrin, casein, and histone yield large amounts of tyrosin and but little tryptophane, while gelatine, elastine, and egg-albumen may yield much tryptophane.

Intestinal putrefaction is dependent on the diet apart from protein. The ingestion of carbohydrate tends to reduce the putrefactive processes. In starvation the putrefaction need not be low. The flora of the alimentary tract is of crucial importance, though as yet little studied in detail. Certain of the actively putrefying anaërobic bacteria produce no indol or skatol but much phenol; the colon bacillus is an active producer of indol. Variations in the flora may be of determining influence in the quantitative relations of the different aromatic substances. The present difficulty in investigation into this question lies in the fact that we have no standards or criteria of what we may regard as the normal flora of the intestine.

There is no constant relation between the protein ration and the output of aromatic substances. No one single aromatic substance bears a constant relation to the total conjugated sulphates; this is to be emphasized for indican. One cannot judge of the total paired sulphates from the indican; one may see high indicanuria with a low total, or high values for the total with but traces of indican. There is no constant relation between the aromatic substances and the bacterial count of the feces. The least faulty method of determining the extent of intestinal putrefaction is by the estimation of the conjugated sulphates. Nevertheless this may yield a totally false interpretation. One sees individuals in perfect health who eliminate large quantities of aromatic substances.

What is then the exact meaning of an increase in benzol derivatives in the urine? A normal output need not indicate a normal state of intestinal putrefaction; an excessive output indicates that more protein than usual is undergoing putrefaction in the alimentary tract. This may be due simply to some individual idiosyncrasy, to peculiarities in the diet, to a heightened virulence of the bacterial flora, to the presence

of a particular bacterium, or to the retention of the food in the tract. Does it necessarily indicate an intoxication? By no means. A certain amount of intestinal putrefaction is normal; an increase may be entirely innocuous. A constant relation between putrefaction and intoxication could hold only if the aromatic bodies were in themselves toxic, if the processes of oxidation and pairing were deleterious to the body, or if the formation of the aromatic substances bore a constant relation to the elaboration of some unknown poison and to the symptoms. There is no evidence that the substances are themselves toxic to any degree, or that the conjugation places any burden upon the body. It is possible that the conjugation with glycuronic acid may be in part reciprocal to the conjugation with sulphuric acid. We have no feasible method of estimating the oxidized aromatic substances. There is no clinical parallelism between symptoms and conjugated sulphates in the urine, either in degree or in the onset and disappearance. What is all along actually assumed is that other substances, poisons, are produced by the putrefaction; and as the degree of putrefaction may be often approximately measured by the aromatic substances, the degree of the hypothetical poisoning is also believed to be so measured.

To recapitulate, a high urinary output of aromatic substances indicates active putrefaction in the colon, which may be innocuous or harmful. A low output need not indicate a low degree of bacterial activity in the intestine, and need not speak against a bacterial intestinal intoxication.

Abnormal Products.—When proteins are subjected to putrefaction, a large number of alkaloid-like substances are formed, commonly termed ptomains. They include a large number of substances of the fatty series, amines, and members of the pyridin and the chinolin series. In addition there are a number of bases, some belonging to the pyridin group, others yielding reactions of chinolin, while still others resemble muscarin. Most of these ptomains are innocuous. None of them except the simple amines have ever been found in the urine or feces of normal individuals or of those suffering from any diseases except cholera, idiopathic cystinuria (occasionally dysentery, enteritis, and obstruction), and true ptomain poisoning due to the ingestion of decomposed protein. It is known from experimental work that time is required for the elaboration of ptomains, particularly the toxic ones; in general no poisonous bases are formed in less than ten days. That these relations are, however, only relative is shown by the fact that in some of the well-studied cases of ptomain poisoning due to the ingestion of decomposed food, the analytically incriminated foods have been but a few days old. We possess no information that in the so-called gastro-intestinal auto-intoxications (the ingestion of decomposed foods must be excluded) ptomains have ever been found. Since a certain decomposition of food occurs within the alimentary tract and the degree of this decomposition may be increased under certain conditions, we are driven to the conclusion (*a*) that there is not time for these changes to proceed to the stage of ptomain formation, or (*b*) the ptomains are decomposed in the system. Either ptomains are not formed in the alimentary tract (apart

from the known instances already mentioned) or they are formed and distoxicated. What evidence is there that ptomains are distoxicated? In experimental work, ptomains are eliminated in the urine just as in idiopathic cystinuria. The general consensus of opinion is that for the diagnosis of ptomain poisoning, the presence of the poison must be demonstrated. Such chemical demonstration has never been accomplished for the class of cases under discussion. The strict conclusion to be drawn from our present knowledge is that the term "ptomain poisoning" should be confined to instances of intoxication due to the ingestion of decomposed food and accompanied by the elimination of the poison, and to instances of decomposition within the tract in which toxic ptomains may be isolated. The presence of cadaverin and putrescin would mean little, for, apart from their harmless roles in cystinuria, they are to be found in old digestion experiments, where they are derived by fermentation of lysin and ornithin, and thus they do not necessarily indicate an abnormal bacterial decomposition. The neurine group has been considered responsible for some of the symptoms of Addison's disease, though without chemical demonstration.

There are several clinical symptom-complexes in which there are reasons of fact and analogy that furnish some warrant for the use of the term gastro-intestinal auto-intoxication. What is needed in these domains is exact investigations—accurate clinical observation and objective chemical research.

Tetany.—Under tetany we understand the full complex, excluding the atypical instances of peripheral or carpopedal spasm. The tetanies associated with extirpation of the thyroid, intestinal parasites, pregnancy and lactation, acute infections, exogenous intoxications, rachitis, and the so-called epidemic or occupational variety, can have no dependence upon the digestive tract.

Typical tetany of the severe form occurring in adults in association with gastric dilatation is rare and very fatal. The dilated obstructed stomach furnishes a most favorable opportunity for the decomposition of food. To determine whether these processes have gone to the stage of the production of poisons, the gastric contents and urine have been investigated. Hyperchlorhydria cannot be incriminated. In a few instances uncharacterized substances have been obtained from the gastric contents (method of Brieger) that were somewhat toxic to rabbits; in other cases the substances were innocuous. From the urine in a few cases, substances have been isolated that gave group reactions of ptomains but were not toxic on intravenous injection into rabbits. Up to the present, therefore, a ptomain poisoning has not been demonstrated for tetany. The tetany of children, associated with gastro-intestinal symptoms and diseases, is often accompanied by acidosis, and an excess of ammonia and of aromatic bodies in the urine. The toxicity of properly prepared extracts from the urine or digestive contents has not been studied. The association with the acidosis is of slight moment, since this is very common in children in subnutrition.

The Alimentary Tract.—Commonly regarded as intoxications are certain gastro-intestinal attacks associated with cutaneous symptoms.

The symptoms are pain, vomiting, often diarrhœa, fever, followed by a general erythema, urticaria, or possibly by other exanthemata. Desquamation may follow. The symptoms in many cases resemble closely intoxication with shell-fish in susceptible individuals, less closely the drug-exanthemata. These attacks tend to recur periodically. Recovery usually follows promptly after gastric lavage, irrigation of the colon, and free purgation. Ptomaines have never been reported in the contents of the tract or urine. The writer is acquainted with one case in which a careful search was made with negative results.

Not infrequently instances of severe violent disturbances of the alimentary tract are observed that bear all the external marks of an auto-intoxication. Usually no adequate cause is to be determined, particularly no gross dietary indiscretion. The attacks consist of sudden vomiting, that may be uncontrollable, extreme pain, profuse diarrhœa in some cases, and in others spasms of the intestine, with meteorism, vertigo, vasomotor dilatation, shock, local spasms, even convulsions and coma. It does not seem possible to consider these as indigestions or infections. If it is possible to exclude exogenous intoxication, the assumption of a gastro-intestinal auto-intoxication is provisionally justified, even though a chemical investigation (which has apparently never been attempted) should fail to isolate any known poison. In all probability attacks of this type are due either to the ingestion of decomposed food, *i. e.*, to exogenous intoxication or are extra-alimentary in origin.

In connection with subacute, complete, or partial *obstruction* of the stomach or intestine, symptoms suggesting gastro-intestinal auto-intoxication are usually noticed. There is fever, albuminuria, headache, insomnia, a marked increase in the aromatic substances in the urine, sometimes exanthematous rashes, possibly severe nervous symptoms, which subside when the obstruction is relieved. The difference in the appearance of patients with gastric carcinoma, before and after gastro-enterostomy, is usually so striking that one is driven to question whether this can be explained by the conditions of nutrition, and is not due in part to the removal of conditions of decomposition in the stomach. Nevertheless the definite demonstration is wanting. In not a few instances of chronic appendicitis, nervous symptoms have been prominent (even epileptic seizures), which disappeared with the removal of the appendix. Admitting the facts, the assumption of a gastro-intestinal auto-intoxication is hypothetical.

Constipation.—The diagnosis of auto-intoxication rests largely upon an excess of indican or conjugated sulphates in the urine. The elimination of indican and of the aromatic sulphates bears, however, no constant relation to the presence or absence of constipation; nor does the degree of increase in the aromatic substances in the urine bear any relation to the intensity of the symptoms. As previously stated, indicanuria is not a sign of auto-intoxication, nor does it afford any index of the elimination of toxic substances. The urine and feces of patients with constipation have been analyzed without success for ptomaines. An illustration of the fictitious value of the interpretation of the symptoms of constipation is afforded by the fact that they are at all times more

pronounced in women than in men, and particularly marked during the menstrual period. It is also noteworthy that many of the symptoms of constipation are to be observed in association with abdominal and pelvic diseases unaccompanied by constipation.

Nervous Dyspepsia.—This has been classed as a gastro-intestinal auto-intoxication. The absence of inflammatory lesions and abnormalities of digestion, apart from variations in the secretion of hydrochloric acid, makes a conception of the etiology of nervous dyspepsia obscure, but there is no good evidence that an auto-intoxication is present. It will not do to say that, since we know of nothing else, it must be an auto-intoxication; if we do not know of anything else and there is no exact evidence of an intoxication, we simply do not know the cause at all. Recently speculation has been rife in this province, and all manner of diseases, from arthritis to arteriosclerosis, have been attributed to resorption of bacterial products. Granting the assumption, discussion of which is not here in place, it is clear that we are concerned with bacterial intoxication, not auto-intoxication.

Nervous System.—For the etiology of a large number of diseases of the nervous system (migraine, neuritis, epilepsy, myasthenia, melancholia, dementia paralytica, psychoses, and even periodic family paralysis) gastro-intestinal auto-intoxication has been invoked. The evidence comprises analogies between these diseases and conditions in the nervous system due to known poisons, the occurrence of constipation and often of an excessive elimination of aromatic substances, the occasional occurrence of acetonuria, the apparent relation of attacks to dietetic errors, the finding in nerve cells of lesions resembling those produced by experimental intoxications, and in the results of the measurement of the toxicity of the urine and, in some cases, of the perspiration. Of exact investigations there are none.

Anemias.—These have long been regarded as diseases of intoxication. The earlier theory of the gastro-intestinal origin of chlorosis is now generally recognized as disproved. For pernicious anemia, however, a good case has been made out. The reasoning does not rest upon such indefinite facts as constipation or diarrhœa, indicanuria, acetonuria. That a persistent hemolysis is at the bottom of pernicious anemia is shown and this is one of our best studied effects of poisons; and, with the demonstration of the occurrence of a severe and persistent hemolysis as the cardinal feature of the disease, a reasonable etiology is established. Earlier work made it probable that the poison was absorbed from the alimentary tract; this has been supported by the experiments with toluylene-diamine, and the analogy with the anchylostoma anemia. It is supported by the histological findings, which indicate that the hemolysis occurs in the portal system, and by the atrophy of the mucosa of the stomach and intestine, so often observed. Concerning the nature of the hemolytic agent we know nothing. A ptomain it certainly is not. For leukemia we have no exact knowledge.

Gastro-intestinal Albuminuria.—The kidneys are sensitive to poisons. In not a few instances of gastro-intestinal disturbances, albuminuria is observed, and it is common in poisoning by shell-fish and decomposed

foods. There can be no strong objection to this classification of the instances of albuminuria that occur in well-defined cases of gastro-intestinal diseases. But to go to the extent of the assumption, without exact evidence, that the so-called idiopathic, cyclic, and recurrent albuminuria rest upon an otherwise unmanifested gastro-intestinal auto-intoxication is unjustified.

ABNORMALITIES IN THE PROCESSES OF OXIDATION

Upon a normal mixed diet, the body heat is largely maintained by the carbonous metabolism; on a protein diet, the protein metabolism may be so exaggerated as to supply the entire heat. The minimum is determined by the amount required to sustain the body temperature under proper conditions of control without food and at complete rest of voluntary movements. Since the body is saving in its metabolism when deprived of food, the figures under these circumstances will be below the real normal; but it is the nearest approximation we can secure. For normal adults the minimum heat values may be given as 10 calories per pound (24 calories per kilo) per day. Elderly individuals may require less, children will require more, emaciated convalescents may maintain a balance upon as little as 7 calories per pound (18 calories per kilo). The average is probably higher, and there are notable individual variations. Less than 10 per cent. of this heat is derived from the combustion of body protein utilized in the daily metabolism. To produce the rest, nearly 17 ounces (500 gm.) of sugar or 8 ounces (225 gm.) of fat are burned.

Under less experimental conditions of life than a fasting repose in a respiration chamber at constant temperature, these figures will be increased. On a usual diet, nearly twice as much protein would be disassimilated, so that a couple of hundred of calories a day would be there added. The heat dissipation will be somewhat increased under ordinary conditions. An increase in oxidation is observed following the ingestion of food, which is marked for protein, much less for carbohydrates and fats. This increase is not slight since the O-input and the CO₂-output after a meal may exceed the fasting figures by 30 per cent., and with forced protein feeding equal the entire fasting oxidation. Digestion is an exothermic process; but since the products must be reconverted, heat will be again absorbed. Peristalsis and the secretion of the digestive juices represent a certain slight heat production. The cleavage, after resorption of the protein, into the nitrogenous and the non-nitrogenous moieties, is held to account, in large part, for this increased oxidation. This specific dynamic action of protein is held to be due to exaggeration of metabolism by the resorbed amino-acids.

Muscular exercise produces a great increase in the processes of oxidation. In the respiration experiment this is limited to the movements of respiration, circulation, and peristalsis. The respiratory movements furnish a considerable percentage of the heat production. Ordinary work increases the oxidation processes by 50 per cent., heavy work may

double the oxidation of the resting, fasting individual. Marked individual variations occur. Exercise of the exhausted muscle especially is accompanied by superoxidation. The velocity of contractions in the unit of time increases the oxidation disproportionately. The weight of the individual is, for obvious reasons, of great influence. Lastly, there is the factor of temperament and facility. Two men of the same stature and weight will not do the same muscular task with the same expenditure of energy. This is not entirely a matter of training; some are, by nature and construction, economical of motion, others extravagant. Restlessness is a factor of influence. These considerations are of great importance; unless constant conditions can be secured, fair comparison between the sick and the well cannot be made.

Under the incidental oxidations are classed those associated with functions that have a *raison d'être* independent of the heat production, such as the protein and nuclein metabolisms. These are increased but slightly by exercise and to some extent by conditions in the diet. So long as the diet contains the normal quota of fat and carbohydrate, less than a sixth of the heat required for the body is derived from these incidental sources. There is a regulatory mechanism in the carbonous metabolism. When the other sources of heat are prominent the combustion of sugar and fat is reduced; but this is a limited adaptation. There is evidence that at higher temperatures, as in the Russian bath, the processes of oxidation in the body are actually increased. In considering the relations of oxidation in disease, we are concerned with the total alone; it is known that a particular oxidation may be increased or decreased in health and disease.

Suboxidation.—Have we evidence of the existence of a state of general suboxidation? The metabolic heat production is derived from the movements of circulation, respiration, and peristalsis secretion, and the reactions of katabolism. The hypothesis of a retardation of metabolism means that these reactions would be accomplished with less consumption of material and production of heat than in the normal. The hypothesis of a retardation of metabolism means that the unit of protoplasm would have a lower level of metabolism. The unit of protoplasm in the cold-blooded animals has a very low level of metabolism, and in the hibernating animal a much lower level than during the summer. The hypothesis of a retardation of metabolism is therefore tantamount to the predication that, as a diseased condition, the unit of human protoplasm can suffer a reduction in the plane of its metabolism. That this is true to a certain extent is illustrated by the economy in metabolism displayed in the chronically underfed. A moderate suboxidation could occur without reduction in the body temperature. There are four directions of heat dissipation: Radiation from the skin, evaporation of perspiration, respiration, and the heating of food and drink to the temperature of the body. The respiratory loss cannot be reduced below the values for the resting individual. The cutaneous radiation and perspiration are subject to a greater degree of regulation, and, with these physical regulations enforced to the maximum, the body temperature of the resting individual could be maintained upon less than the minimum values given. On how

much less we do not know. Since, however, the body temperature is normal in individuals suspected of having suboxidation, the argument is concerned with just this fraction. A reduction of the body temperature would not in itself indicate suboxidation.

That such a state of suboxidation exists as an acute condition may be assumed, though no accurate studies of appropriate cases exist. In prolonged surgical anesthesia and drug narcosis, following extreme hemorrhage, in shock, in asthenic infections, in terminal diabetic and cholemic coma, such a condition probably exists. In these states the body temperature is low. This may be due in part to excessive heat dissipation, since many have extreme vasomotor dilatation. The renal functions are nearly abolished and analyses of the urine indicate a very low protein katabolism, far below that of starvation. The whole picture suggests prostration of all the vital functions, including that of systemic oxidation. The state is one adjacent to death and can be tolerated but a few hours.

In connection with chronic diseases, the use of the expression may be controlled by investigations, and, though these are very onerous, enough cases have been carefully studied to enable us to form a tentative judgment in the matter. There are four groups of chronic diseases in which suboxidation has been considered; obesity, the anemias, myxœdema, and cachexia strumipriva, and the cachexia of malignant diseases. The facts to be determined are: What is the condition of the nitrogenous and carbonous metabolism, how is the O-input and CO₂-output, the heat production?

Obesity.—Is there suboxidation in obesity? Preliminary to this question a consideration of the relations of the sexual functions to metabolism is important. Castrated animals are more easily fattened than their normal fellows. In young animals the growth comprises a flesh- as well as a fat-mast. The question whether this rests upon a reduction in the oxidation processes is of great importance, because if it should be demonstrated that the plane of oxidation may be shifted by castration, the sexual glands would acquire a metabolic function allied to that of the thyroid and the pituitary body. Castration in animals converts a nervous into a phlegmatic temperament, and we know that the nervous temperament is wasteful in movements, metabolism, and combustion. There is an actual loss of material attending the functions of the organs of reproduction, though we have no way of estimating it. The sum total of these influences is sufficient to account for changes of notable degree, though a measurement is impossible. In the end the decision must be left to metabolic experiment.

Years ago investigations were believed to have shown that the oxygen consumed by castrated animals was nearly 20 per cent. less than the amount consumed by the control animals. The methods were faulty, the experiments brief, and the results excessive; such a degree of suboxidation would lead to the development of the highest degree of obesity within a very short time. Recently the work has been repeated with longer periods of observation; a positive evidence of suboxidation has not been obtained. Castrated dogs of both sexes (and unsexed women)

exhibit the same carbonous and nitrogenous metabolism as the properly managed controls.

Coming to the question of obesity, there are two groups of fat people that present symptoms suggesting an abnormal metabolism: The excessively fat children, and those adults who, leading active muscular lives and not being addicted to excesses in eating and drinking, become pathologically obese. There are two ways of investigating these cases: The method of metabolic and combustion experiment, and the method of prolonged observation on a known and controlled diet, with careful observation of the body weight. In metabolic experimentation, one must realize that much lower values will be secured than in thin individuals, without affording any basis for induction. The unit of substance necessary for a body is related only to the mass of the metabolic tissues. The bones, apart from the marrow, are practically of no metabolic moment; but since they remain constant with respect to obesity, need not be considered. Little energy is required for fatty tissue. When an individual weighing 160 pounds (70 kilos), in good nutrition, adds fat up to 220 pounds (100 kilos), his metabolic transformations will not increase in the ratio of 16 to 22; the stout man will have about the same metabolism that he had when thin, and the unit of calories of O-input and CO₂-output per kilo weight will have decreased. To be of positive value the variations must exceed these relations. The results of the combustion-metabolism of cases of obesity have been negative—no evidence has been obtained that there is any reduction in the processes of oxidation. There are a few reported cases in which obese subjects have maintained their weight on a diet of very low caloric value (as low as 1000 calories). It is unfortunate that such an individual has not been placed on a respiration experiment.

Myxœdema and Cachexia Strumipriva.—The evidence bearing upon suboxidation in these diseases may be grouped under four headings: (a) The direct combustion experiment. In one case of sporadic cretinism the values, though low, were within the normal. (b) The clinical symptoms. The patients incline to low body temperature despite the fact that, on account of the almost complete abolition of perspiration, the heat dissipation seems below the normal. These facts, while suggestive, do not directly indicate the existence of suboxidation; they indicate that the subjects have lost in part the power of suddenly increasing their combustion to meet the demands imposed upon it. (c) The results of thyroid medication. These are striking, but they bear only in part upon this question. The administration of thyroid preparations in the healthy, and to a greater extent in the myxœdematous, results in a marked increase in the protein katabolism and to some increase in O-input and CO₂-output. The increase of the combustion may be as high as 15 or 20 per cent. (d) The contrast between myxœdema and cachexia strumipriva, and exophthalmic goitre. Increase in the nitrogenous and carbonous metabolism is the striking metabolic symptom of Graves' disease; it is relieved by extirpation of the thyroid. Myxœdema associated with atrophy of the thyroid and cachexia strumipriva due to total extirpation of the thyroid are relieved by thyroid medication.

The inference is tempting, nevertheless the facts do not establish a suboxidation. The fact that on administration of thyroid preparations a certain exaggeration in combustion occurs, is not proof that, with the atrophy of that organ, the combustion would fall below the normal.

Anemias.—The essential anemias were long held to be associated with suboxidation. It seemed natural to question whether an adequate quantity of oxygen could be transported by such small quantities of hemoglobin. The experimental studies have given the answer in the negative. Under proper conditions of control, subjects with chlorosis exhibit a normal protein and carbonous metabolism, while cases of pernicious anemia and leukemia display excesses in the protein metabolism and normal, or supernormal, oxidation. The work of circulation and respiration is notably increased in these subjects.

Cachexia and Marasmus.—One not infrequently meets with instances of these conditions that suggest suboxidation. The patients become emaciated to the last degree, the condition seems to become stationary and for weeks the patients remain in a scarcely more than hibernating existence. The body temperature is low, the skin dry, the extremities cold, there is scarcely any digestion, and yet life is prolonged in a most remarkable manner. That their metabolism and combustions are low is not to be doubted, but it is questionable whether they are lower than in simple chronic subnutrition. Individuals subjected to prolonged subnutrition become, in a sense, inured thereto and exhibit a nitrogenous and carbonous metabolism notably lower than in acute starvation. There is nothing to indicate that in the conditions of marasmus and cachexia the relations are different or more extreme than in simple chronic subnutrition, and, although the body under these circumstances operates very economically, we cannot speak of suboxidation.

The hypothesis that diabetes, gout, the so-called lithemic diathesis, the chronic arthritides, asthma, migraine, eczema, and other diseases of unknown etiology are manifestations of a retardation of metabolism is devoid of foundation.

Superoxidation.—Under this term we understand an increase in combustion in excess of the caloric demands of the body. There are oxidations in the protein metabolism, but the chief reaction is hydrolytic cleavage; and oxidation of the products of the hydrolytic cleavage of protein can scarcely be conceived to be susceptible of an exaggeration in the direct sense. Thus, oxidation is a secondary process in the metabolism of protein, and as such is not susceptible of a primary exaggeration, though it might be subject to a primary retardation. Superoxidation affects directly the sugar metabolism. If the carbohydrate input be not sufficient, the fat combustion will become exaggerated so soon as the body glycogen has run low. If the fat ingestion be not sufficient to the oxidation, the body fat will be burned. Since we regard these combustions as of the nature of ferment reactions, the pathological exaggerations are naturally and logically to be ascribed either to an increased concentration of the substrate, or to an excess of the ferments. It is seen to some extent in most instances of fever, though not the cause

of fever. It is present in diabetes, and probably in most infections, malignant disease, or metabolic diseases of serious degree.

Deficiency of Oxygen.—Asphyxiation is the result of lack of oxygen. Many exogenous intoxications act in part by preventing the utilization of oxygen; such are the nitrites, morphine, arsenious acid, carbon monoxide, cyanides, chloral, paraldehyde, veratrine. A marked degree of deficiency in oxygen cannot be borne for more than a short time. One hears a great deal of the deficiency of oxygen in the production of disease, but when the evidence is analyzed it is very scanty. To establish a lack of oxygen, one should possess gas analyses of the respiration or blood. Breathing an atmosphere low in oxygen is accompanied by a high respiratory quotient. In acute pneumothorax and cardiac dilatation, the body suffers from lack of oxygen; the blood content of oxygen and carbon dioxide falls. This situation cannot be long maintained; if compensation be not rapidly established death occurs. In acute and massive hemorrhage a deficiency occurs; this cannot, however, be due to the reduction in the red corpuscles, for it is not possible to bleed an animal over 40 per cent. of its blood if the fluid be replaced, and there is no deficiency of oxygenation in such a degree of anemia *per se*.

As a subacute condition, there is little evidence that a notable degree of deficiency in oxygen occurs in severe cardiac and pulmonary diseases. In these diseases the efforts at compensation usually are practically successful; what so often kills is the exhaustion produced. In these one may observe an excess of protein katabolism and the appearance of lactic acid in the urine. In some instances of heart disease the blood contains more CO_2 and less O than normal. A favorable tension of O and CO_2 can be shown to exist in the alveoli of the lung, despite which the blood does not seem able to cast out the normal amount of CO_2 or absorb the normal amount of O. Whether the fault lies in an alveolar induration or in a slowing of the circulation is not known. It does not lie in a deficiency of the respiratory movements. It is not now believed that such increase in CO_2 in the body is harmful.

Just how the partial lack of oxygen affects the organism is not well known. The loss falls first on the protein metabolism, the intermediary products of which appear unoxidized in the urine. The protein katabolism is exaggerated. The body attempts to make up for the deficiency by the utilization of intramolecular oxygen; to what extent this can compensate is not known. In animals under carefully selected conditions of experimentation an acidosis may be produced. In the anemias, cachexia, and tuberculosis, in which a deficiency of oxygenation has been popularly supposed to exist, the consumption of oxygen is either normal or excessive. It is possible that exercise would lead to a temporary relative deficiency of oxygen, but under conditions of rest there is no such deficiency.

DISTOXICATION

Under distoxication are grouped those acts of metabolism by means of which endogenous toxic substances are rendered innocuous. The

known reactions of distoxication include conjugation, oxidation, and reduction. Some of the products of the digestion of protein are quite toxic, yet in the liver this is nullified. The general application of the theory of distoxication lies in the proposition that the intermediary products of metabolism are more or less toxic and that in the completion of the processes of metabolism to end-products we have what in effect has the value of a distoxication. When also abnormal intermediary products of metabolism appear, they may be distoxicated. Thus cations are withdrawn from the tissues to combine with the anions in experimental acid poisoning, in the acetone acidosis, and in connection with an ash-free diet. When glycuronic acid is derived from glucose it is paired in the body. If leucin and tyrosin are formed by an abnormal intermediary protein metabolism, they will be oxidized to phenyl-oxy-acids; should the amount of the amino-acids be large, a certain rest will be eliminated unchanged. In an analogous sense we may speak of cystinuria and alkaptonuria as abnormalities of distoxication. Elimination is obviously an indispensable adjunct to distoxication. Some substances that cannot be chemically distoxicated are harmless if promptly eliminated. The general tendency has been to concede the relative innocuousness of the end-products of metabolism and to refer auto-intoxications rather to deviations in, or the non-completion of, the intermediary processes of metabolism.

RETENTION INTOXICATIONS

Under this we understand the retention of the normal end-products through insufficient excretion. This leads to accumulation of these substances, and the intoxications are due to their influence upon various tissues and functions. We ought to separate the retention of an excess of a normal substance from the accumulation of an abnormal substance.

Jaundice.—It may be accepted that, with the exception of cholesterol, no specific organic constituent of bile is normally present in the tissues. The biliary constituents that may be held responsible for the toxic action of bile are the salts of the glyco- and tauro-cholic acids and the pigments. Glycocoll and taurin are products of protein hydrolysis; the derivation, as well as the chemical nature, of cholic acid is not known. Since the liver is the seat of the final disintegration of hemoglobin, it has been assumed that the glycocoll and taurin are derived in part from the hydrolysis of the protein moiety in hemoglobin. The pigments are derived from the hemoglobin.

The toxicity of bile lies largely in the biliary salts, although the pigments possess a certain toxicity, especially evident in the depression of the body temperature. Bile acts as a tissue poison, particularly to the renal, hepatic, and muscle cells. There is further evidence that it exerts a hemolytic action. Possibly this may be related to the hemorrhagic tendency so frequently noted in jaundice. The body temperature is reduced, the pulse and respiration retarded—apparently on account of peripheral influences, since the effects occur following the local appli-

cation of bile to the surface of the heart after section of the vagus in the curarized frog. There is dilatation of the peripheral capillaries. Large doses cause coma, convulsions, and paralyses. In jaundice we observe clinically, retardation of the pulse, somnolence, albuminuria, sometimes emaciation and cutaneous disturbances, occasionally hemorrhages—directly corresponding to the experimental findings. In simple instances of jaundice the digestion is little impaired. The temperature of the body may be normal or slightly reduced. Usually there is little disturbance in the nitrogen metabolism, nutrition, or body weight. In prolonged cases the functions of the liver may be greatly impaired, the glycogen of the muscles, as well as of the liver, may be practically absent, and the epithelial cells extensively degenerated.

Quite inconclusive is the relationship of hepatic coma to jaundice. Symptomatically the so-called cholemia resembles experimental biliary intoxication, but the same symptoms are as frequently seen in hepatic cirrhosis without jaundice. It is difficult to understand how so many individuals bear jaundice without marked toxic symptoms. The common explanation, that in one case the renal elimination of the bile is sufficient, in another insufficient, is not borne out by urinary observations. In all likelihood the cause of hepatic coma is to be sought less in the toxic effects of the circulating bile than in a disturbance of the metabolic functions of the liver, just as in acute yellow atrophy, phosphorus poisoning, experimental ablation of the liver, and anastomosis of the portal vein and inferior cava. Under this interpretation the prolonged jaundice could lead to grave auto-intoxication through abolition of hepatic function.

Retention of Carbon Dioxide.—Is there an intoxication with metabolic carbon dioxide, connected with disturbances of the circulation and respiration? There is the greatest discrepancy between the apparent simplicity and the actual complexity of the problem. The actual problem must be first defined. (a) The gas-exchange of the body has no necessary relations to dyspnoea. Many forms of auto-intoxication, in which the gas-exchange is not in the least concerned, give rise to dyspnoea; such are diabetic coma, uremia, hepatic coma. Bacterial toxins cause dyspnoea, as seen in pneumonia. (b) Intoxication with carbon dioxide is not necessarily associated with cyanosis, since the fault may lie entirely within the internal respiration. (c) There is no necessary association between the gas-exchange and the carbon-dioxide content of the blood. It is possible for the O-input and the CO₂-output, and heat metabolism to be normal, while the blood is surcharged with carbon dioxide and the cyanosis pronounced. (d) Lastly, deficiency of oxygen must be separated from an excess of carbon dioxide. This is often extremely difficult. Carbon dioxide is the normal stimulus to respiration. When the blood is rich in CO₂, respiratory activity is vigorous; when the blood is poor in CO₂, respiration is weak. These facts have been brought lately into relation to surgical shock.

In what diseases and under what circumstances is there an excess of carbon dioxide in the blood and tissues, and what degree of such excess may be properly said to cause auto-intoxication? Oxygen is carried

in the blood in chemical combination with hemoglobin, in small part by physical absorption in the cells and plasm. The arterial plasma is saturated with oxygen. Arterial blood contains about 20 vol. per cent. of oxygen, venous blood some 8 to 10 vol. per cent. In death by suffocation the oxygen is decreased before death to less than 1 vol. per cent. The relations of the carbon dioxide are less certain. It is present in arterial blood to the extent of 30 to 40 vol. per cent., in venous blood about 10 vol. per cent. more. Five-sixths of the gas is in the plasma. In asphyxiated animals the concentration of CO_2 in the venous blood rises but little above the maximum normal of 50 vol. per cent.; this is comprehensible when we realize that most of the oxygen contained in the body is held in the tissues. Since the stay of the blood in the tissues and lungs is so very brief, association and dissociation must occur with great rapidity. Since the reaction of the blood is neutral, no process can be assumed that is chemically incompatible with this neutrality.

In asphyxiation the blood-content of CO_2 is increased from one-fourth to one-third, the oxygen-content falls to a trace. Death is due to lack of oxygen and not to the excess of CO_2 . If an animal be placed in an atmosphere containing 20 per cent. or more of O, 76 per cent. of N, and 4 per cent. of CO_2 (the quantity in expired air), death will occur after a period of narcosis and this represents true CO_2 poisoning. If an animal be placed in an atmosphere too low in oxygen, death will result after a time and the blood will contain less CO_2 , as well as less O than normal.

Do disturbances exist in disease which act to reduce the expiration of CO_2 more than the inspiration of O, to the end of CO_2 congestion in the blood? What is the extent of such CO_2 congestion? The conditions are divided into two groups: those in which the respiratory surface is diminished and those in which the action of the heart is disturbed. Recent studies in the physiology of combustion have taught us the extent of the powers of adaptation and compensation residing in the organs of circulation and respiration. In all probability, until these limits are reached, until the unit of blood is not aerated in the unit of time, an auto-intoxication is not to be apprehended. It is indeed probable that deficiency in CO_2 in the blood may be a more serious state than excess of CO_2 .

Of gas analyses, either experimental or clinical, we have few, but it is fairly certain that several conditions may be found: (a) The O-input and CO_2 -output and the content of the blood in the two gases are normal. This has been found in several cases of emphysema and of heart disease, and indicates a complete sufficiency of the efforts at compensation. (b) The O-input and CO_2 -output are normal, but the CO_2 content of the venous blood is excessive. This has been noted in experimental disturbances of respiration, and indicates that the efforts at compensation were successful only when the level of CO_2 in the venous blood was raised. (c) The O-input is normal, the CO_2 -output reduced, the CO_2 in the venous blood not increased. This has been found in some experimental pneumonias. (d) The O-input and CO_2 -output are reduced. The CO_2 is increased and the O reduced in the blood. This has been found in several cases of heart disease. (e) The O-input is much reduced, the CO_2 -output reduced, the O in the blood much reduced, the CO_2 not

increased, possibly reduced. This has been found in some instances of experimental pneumothorax. CO_2 intoxication could appear in (b) and (d) alone; intoxication from deficiency in O could occur in (d) and (e). Cyanosis is a sign of lack of O rather than of congestion with CO_2 . Considering the marked powers of adaptation and compensation, what we most need are repeated gas analyses to show what degree of reduction in O-input and CO_2 -retention in the blood exist, and with what symptoms and signs they are associated. In diabetic coma the CO_2 content of the blood is greatly reduced.

In the ordinary cases of the types under consideration, the combustions of the body are normal. This does not indicate that there is no CO_2 congestion—the overflow of a stream will be the same over a high as over a low dam. It does, however, indicate that the input of O is adequate and the total combustion normal; if these subjects are intoxicated it must be from simple CO_2 -retention. In acute experimental dyspnœa the protein metabolism is abnormally increased, the result of deficient oxygenation. The urine contains glucose and lactic acid, the results of lack of oxygen.

In all these there is little to suggest that the subjects are in a direct sense suffering from intoxication with CO_2 . It is not to be positively denied that there is an intoxication with CO_2 in these diseases, but we should realize how scant is our information of the actual conditions, and how indefinitely it points to such an intoxication. The CO_2 -content of the tissues is known to be much higher than in blood. We do not know that in any circulatory or respiratory diseases the blood-content rises to the height of the tissue-content, or that the latter is increased.

Retention of Perspiration.—The natural interpretation of the cause of death from extensive superficial injury to the skin, as in burns, rests upon the abolition of the cutaneous function. The chief symptoms are quite like shock. They are not due to the retention of the normal perspiration, as the sweat is almost free of toxic action. The retention of water could not account for the symptoms, nor the salts and organic substances known to be eliminated through the skin in the quantities and time concerned. That the simple retention of perspiration cannot be the factor is shown by the experiments in which nearly the entire bodies of men were covered for days with rubber plaster and collodion, without producing any symptoms or signs of illness whatever. That rabbits die after being coated with varnish has been explained as the consequence of the paralysis of the vasomotor system, whereby the heat dissipation is exaggerated beyond the power of compensation.

We are thus driven to the assumption that widespread lesions of the skin cause disturbances in metabolism, which, acting with the disturbances in the vasomotor system, lead to the rapid collapse. That toxic substances are at work is shown by the widespread hemolysis, the acute degenerations of parenchymatous and muscular cells, and the rapid onset of these lesions and of the clinical symptoms. The hypothesis that the coagulations occurring in different parts of the body are due to an excess of fibrin ferment has not been proved. A burn must have a certain superficial extent in order to be fatal. Thromboses are promi-

nent in the pulmonary vessels, and these have been held to lead to an acute venous congestion and arterial anemia. Acute venous congestion and arterial anemia due to other causes, however, do not produce the symptom-complex observed in burns. The shock of burns is very similar to the state of anaphylaxis, and investigation of the latter may be expected to illuminate the former. The serum of burned animals is toxic on parenteral introduction into normal animals. Dimethylguanidine has been suggested as the toxic agent.

Retention Intoxication of Intestinal Origin.—Under a strict interpretation of the term, we have no evidence that such a thing as a retention of the intestinal excretion exists. The feces contain the undigested and unabsorbed residue of the food; the alimentary juices; bacteria and the products of their metabolism; the unabsorbed gases of the atmosphere, mostly nitrogen, and the gases of fermentation and putrefaction; the unabsorbed salts of the diet, and the salts eliminated from the tract and glands; and a small, though undetermined, quantity of metabolic products. The bulk of the feces is water and bacteria. Of the nitrogen of normal feces, that of the digestive juices may comprise as much as one-half. Now the alimentary tract is, from the metabolic point of view, outside the body. The only true retention intoxication would therefore be such as results from the non-secretion of salt and the juices of the tract and the different glands. Non-secretion of the gastric juice occurs as a nervous abnormality, independent of any lesion; it is not accompanied by signs of auto-intoxication. Of the non-secretion of the succus entericus we know nothing. Eliminations of excretions stand obviously upon a totally different footing as regards their relations to auto-intoxications than the eliminations of secretions of physiological function. Abolition of the one results in a damming back; abolition of the other simply in the cessation of the particular function associated with it, though this may entrain a secondary auto-intoxication. The digestive juices in the lower intestines, after their functions are completed, are themselves the prey of putrefactive bacteria, and from this time are apparently to be ranked with the unabsorbed protein. A retention intoxication from non-elimination of salts, particularly of iron and lime, is inconceivable. Of an intoxication resting upon the non-elimination of metabolic products we have no knowledge.

All of the so-called retention intoxications of the alimentary tract are, so far as we have reliable evidence, due to the action of bacteria. Some foods are primarily toxic, others are directly indigestible. These and the bacterial decompositions should not be classed as retention intoxications.

Suppression of Urine.—Under this term we understand the non-secretion of urine. The hypothesis that uremia is simply a retention intoxication, the result of the non-secretion of the urine, is incompatible with a number of well-determined facts. With healthy kidneys, complete suppression is usually without any immediate symptoms of intoxication. In renal disease there is no parallelism between uremia and retention. There are periods of almost complete anuria in subacute nephritis without symptoms of uremia. Often in subacute nephritis anuria and uremia go together, but many exceptions occur. A nephritic or cardio-nephritic

patient, dropsical to the last degree but free of uremia, may be freed of his dropsy only to develop uremia. The hypothesis is advanced that the diuresis, purgation, or diaphoresis, have brought into the circulation the poisons that lay concentrated in the tissues. This explanation will not hold, for unless it be shown that there is some coefficient of distribution to account for such localization of the urinary constituents, we cannot with our knowledge of the circulation and of the laws of diffusion believe in it. Certainly if that explanation be true, the treatment of the uremic attack by purging and sweating is dangerous.

One reads a great deal of the retention of particular constituents with elimination of the water. Obviously such a condition could be but transient for the electrolytes, because it would soon lead to a condition of hypertonicity that we know to be impossible. The organic constituents could be much longer retained without disturbing the osmotic conditions to a notable degree. There is often retention of urea in nephritis, more often of uric acid, while retention of rest nitrogen seems especially prominent. There may also be hyperglycemia. It is possible that these retentions are related to the hypertension, vascular disease, and cardiac hypertrophy of chronic nephritis. But it seems certain that these retentions do not represent direct intoxications and are not related to uremia.

A general consideration against the theory of simple retention is that it lays upon the kidneys no blame but that of a stoppage of the elimination; it reduces nephritis simply to a plugging of a filtering membrane. Experience with nephritis surely suggests that the disturbances are more than a simple reduction in the power of elimination. Our knowledge of the toxicity of the normal urine does not support the idea that a simple retention would lead to an intoxication. The toxicity of the urine depends upon the fact that the urine is a hypertonic solution rich in potassium salts. Even this toxicity will practically disappear if the rate of injection be so slow that the cells have an opportunity to accommodate themselves to the new conditions. The urotoxic coefficient of Bouchard, as determined by the intravenous injection of urine into animals, is worthless.

From the wider theoretical point of view, one can understand how a retention of urine could lead to disturbances in metabolism. If the organic constituents were retained to a greater degree than the water, the result would be to increase the concentration of those substances in the body. Now the processes leading to the formation of these urinary constituents may be assumed to be of the nature of ferment reactions. The obvious result of an increase in the concentration of the products of the reaction would be to retard the reaction, that is, to retard the rapidity of katabolism, and in addition to afford opportunities for qualitative variations.

SALTS, ACIDS, AND ALKALIS

The proper study of the relations of acids, alkalis, ions, and salts by physicochemical methods is quite recent. That they must possess

relations of the greatest importance in disease may be confidently assumed. Of direct data almost none are available. Indeed, little of our present knowledge has been derived from studies on higher organisms. At present our knowledge of the relations of salts, alkalis, and acids in endogenous intoxications is limited to acidosis.

Acidosis.—Under this term we group the disturbances in metabolism that result from the predominance of acids in katabolism. There is in the carnivorous organism always some such predominance, but one easily compensated for. The chief sources of acid are the following: (a) The acids of carbohydrate fermentation in the alimentary tract. (b) The sulphuric and phosphoric acids derived from the katabolism of common protein and nuclein respectively. (c) Lactic acid. (d) The members of the ketone group, diacetic and beta-oxybutyric acids, derived from the fats. (e) Other acids formed in the body—glycuronic, oxalic, uric, aromatic oxy-acids, carbamic acid, and carbon dioxide—are apparently never concerned in the production of an acidosis. For the neutralization of these acids we have the excess of alkali contained in the mixed diet and in drinking-water; when these are insufficient, the fixed cations of the body and the ammonia of the metabolism. Obviously an acidosis may be inaugurated either by a deficiency in alkali or an excess in acids. The result will be the same whether acid be ingested or formed within the body. The tissues and fluids of the body do not become of acid reaction in acidosis; this is prevented by the physicochemical relation of monobase to dibase phosphates and of bicarbonate to carbonic acid.

Experimentally an acidosis may be produced by the use of an ash- and alkali-free diet. Under these circumstances the sulphuric and phosphoric acids must combine with fixed cations withdrawn from the tissues, and ammonia withdrawn from the urea metabolism. After a certain number of days, no matter how normal the diet in other respects, severe symptoms appear in the peripheral neuromuscular and central nervous systems, followed by death. In simple starvation the degree of acidosis is not marked, since the protein katabolism is low. Acidosis could occur only very late in a protein-free diet, since here too the protein katabolism is low. The human body cannot maintain the daily katabolism of a hundred grams of protein in the absence of ingested cations without the development of an acidosis within a fortnight. In a similar manner, if a mineral acid be administered in quantity equal to that daily formed in the average metabolism, an acid intoxication will develop after a few days.

The acids of carbohydrate fermentation are rarely of pathological importance; they are easily oxidized and are rarely formed in quantities so large as to constitute a menace. There is, however, a possibility that these acids may be responsible for some of the attacks of acidosis seen in childhood. Lactic acid may be derived either from protein or carbohydrate, and is an intermediary product in the oxidation of glucose. It may theoretically be derived from the oxy-acids of the fatty acid series. In disease, it seems usually to have been derived from protein or sugar. The lactic acid formed within the alimentary tract is apparently

not a cause of acidosis. Most important are the members of the acetone group, which are most often concerned in the production of an acidosis.

The ill effects of acidosis are not clearly understood. There are several chemical possibilities:

(a) Acidosis may act simply by virtue of acidity, which is a remote possibility. That the blood may become acid shortly before the death of an animal with sulphuric acid poisoning, has been demonstrated. In any event, an acid reaction of the blood could be only a terminal phenomenon.

(b) Acidosis may act through cation withdrawal. The reserve of cations in the body is limited. It is a postulate of physiology that there are cation-protein complexes in protoplasm. Very soon the supply of fixed cations is greatly reduced or fails, and from thence ammonia remains to combine with the acids. Ammonia does from the very beginning combine with a portion of the acid. What we do not understand are the relations of the ammonia to the fixed cations in the neutralization of the anions; no regularity is apparent in the fluctuations clinically observed. How the cation withdrawal results in symptoms is totally obscure. It may be said that the withdrawal of fixed cations leads to protoplasmic disintegrations; but from such statements we obtain no exact or definite ideas. If the withdrawal of the cations be the condition underlying the symptoms of intoxication, one does not understand those cases in which the symptoms appear suddenly without having been preceded by a period of cation withdrawal. That the administration of alkalies does not always result in amelioration is no argument for or against this factor.

(c) The acids may possess a toxicity *per se*. A certain toxicity has been made probable for the salts of β -oxybutyric and diacetic acids. Normally the body possesses the power of oxidizing large quantities of these acids. In diabetes the body has lost, in part, its power of oxidation.

(d) Lastly, the toxic effects of acidosis may be related to disturbance in the concentration of carbon dioxide in the blood and tissues. This result is especially to be observed in severe diabetic acidosis.

AUTO-INTOXICATIONS ASSOCIATED WITH PROTEIN

The digestion of protein is an act of hydrolysis; the end-products are amino-acids. It has been shown that animals may be maintained in nitrogen balance on a diet whose sole nitrogen is present in the form of amino-acids. Under exceptional circumstances, native protein may pass through the intestinal mucosa into the circulation. The higher albumoses are absorbable; secondary albuminoses and peptones are readily absorbed. The processes of nitrogenous katabolism may be discussed under the end-products, urea, ammonia, purin bases, and creatinin. The purin metabolism is really separate from the common protein metabolism and will be considered by itself.

Urea.—Protein katabolism is chemically very similar to protein digestion. In metabolism, as in digestion, the end-products of the hydrolysis are amino-acids. In the aseptic autolysis of organs and in the rapid degeneration of tissue, amino-acids are found in large quantities.

It must be further assumed that the dynamic factor is a ferment accelerating a slow hydrolysis that can be demonstrated to occur whenever protein and water are mixed. The products of protein hydrolysis are subject to a variety of reactions—disamination, oxidation, anhydration, and reduction. It is obviously possible that these secondary reactions might be disturbed or insufficient, but our knowledge of these, in so far as they concern the elaboration of the nitrogen, is confined to the steps by which urea is formed from amino-acids.

The liver is the chief seat of urea formation. Perfusion of the liver with the vegetable salts of ammonia, in particular the lactate, carbamate, and carbonate, with the monamino-acids that are formed in the hydrolysis of protein, or with the diamino-acids like arginine, will result in the formation of urea. Liver pulp is able to convert these several substances into urea. There can be little doubt that these reactions are fermentative, and consist of disamination and oxidation. Some ammonia comes to the liver through the portal vein, some is formed in the liver, and a certain amount of amino-substance is withdrawn from the muscles by the venous blood. On purely theoretical grounds it would seem that most of the material should come to the liver from the general system through the arterial blood and that it should come in the form of amino-acids and as salts of ammonia.

The liver is not the sole seat of urea formation; the excretion of urea never disappears entirely after extirpation of the liver or its exclusion from the portal circulation; to a certain extent the reactions probably occur in all tissues. That the kidneys are prominent in the synthesis of urea is not demonstrated.

Ammonia.—The ammonia of the urine was once supposed to bear a reciprocal relation to the urea. According to this idea, if the diet was rich in vegetable salts of the fixed alkalis or in ingested fixed alkali, the urine would contain little or no ammonia; if the diet was poor in fixed alkalis or their vegetable salts, the urine would contain a large amount of ammonia, this being withdrawn from the urea metabolism to combine with the sulphuric and phosphoric acids derived from the oxidation of protein and nuclein respectively. Of the importance of this factor there is no doubt, but it is not the sole factor. The formation of diacetic and β -oxybutyric acids in the intermediary metabolism is associated with an excess of ammonuria and may, indeed, except insofar as the acids are reduced to acetone, be measured by it. Ammonia is also absorbed from the intestine. The absorption from the alimentary tract of the acid products of fermentation is accompanied by the binding of ammonia, of small moment normally. The formation of urea is to be regarded as the conversion of ammonium salts into urea under the influence of enzymic acceleration, and a certain amount of ammonia remains in the circulation for the simple reason that the reaction is an incomplete and reversible one. Ammonia circulating in the blood-plasma would naturally be eliminated by the kidneys. The elimination of ammonia is subject to rather marked fluctuations, even when the subjects are upon a constant diet. Marked pathological augmentations are in all probability connected always with ketonic acidosis.

Creatinin.—Blood and muscles contain small quantities of creatinin and of the parent substance, creatin; the urine contains creatinin alone; creatinin of urine is identical with that of muscle. Creatin on administration is eliminated in part unchanged, in part as creatinin; a fraction however is lost in the metabolism. The natural interpretation of these relations would be that creatin is formed from some protein of muscle and then converted into creatinin. The amount of creatin and creatinin is greater in the exhausted than in the resting muscle, but this does not appear to show itself in the total nitrogen or creatinin output. The creatin-creatinin metabolism is specific to the muscular system and is independent of the common protein metabolism. Creatin appears in the urine in place of creatinin in part when the power of burning sugar is impaired.

Disturbances in the Protein Metabolism Dependent on the Input.—A diet devoid of protein means nitrogen starvation. If carbohydrate and fat be present in excess of the quota required for the maintenance of the body heat, the nitrogen output (urea) will sink far below the output in starvation. Insufficiency of protein is unfortunately of frequent occurrence. Whether any people live for any length of time upon a ration containing less than 1 ounce (30 gm.) for a body weight of 150 pounds (65 kilos)—the lowest known experimental figures—is not known. The results lead, so far as we know, to no auto-intoxication. Subnutrition is of grave consequences to children, less harmful to the aged. The most prominent result is the lowering of the resistance, particularly to the infections (starvation may be shown in animals to be accompanied by a reduction in the antibacterial properties of the blood). Important is one metabolic sign which those underfed in protein share with the convalescent—the retention of nitrogen on a ration that would not be sufficient to maintain a balance in the same individual in health and good nutrition.

The results of an excess of protein have not been fully investigated. A man of 160 pounds (70 kilos) can digest probably not over 2.2 pounds (1 kilo) of protein per day. When an individual in good nutrition is placed upon a heavy protein diet, the usual result is that katabolism is exaggerated, so that the output equals the input and the body is upon a nitrogen balance. Under forced feeding with carbonous as well as nitrogenous food, an appreciable retention of nitrogen may occur. This is not permanent for the healthy adult; it disappears after the forced feeding is suspended, the products being eliminated in the urine. Such a retention of nitrogen is very easy to attain in children, but here it is partly permanent, representing a true flesh-mast. The same thing is true to some extent of convalescents; until they have regained their normal musculature and body weight, the retention is likely to be permanent.

This retention is in the form of protein. The protein of the blood plasma is not a constant but a fluctuating quantity, being lowered in sickness and subnutrition and raised in supernutrition. In part, the excess of protein is carried in the tissues, especially in the muscles, which seem to possess powers of compensation. The muscle cells shrink in sickness and chemical analyses have shown, under these circumstances,

a reduction in the nitrogen and an increase in the water. Supernutrition will result in an increase in the size of the muscle fibre, and an increase in the nitrogen and a reduction in the water. This retention simply indicates an excess in the individual's powers of digestion and absorption over the power of disassimilation; when the input falls below the level of katabolism, the excess will be gradually removed until the individual is restored to the natural balance.

Does the excessive ingestion of protein lead to abnormalities in the metabolism to auto-intoxication? There is current an idea that the heavy consumption of protein is harmful. It is supposed to be responsible for gout, innumerable ill-defined diatheses, arteriosclerosis, nephritis, a large number of skin diseases, and, by the extreme vegetarians, for an intoxication *sui generis*. For all these claims there is no adequate basis. The excess of protein is hydrolyzed, the body displays the greatest vigilance in keeping the system in a nitrogen balance. With an increased protein ration the protein residue in the intestine is increased, affording a greater substratum for putrefactive processes. The products of the excessive protein metabolism have all to be eliminated, and this imposes an increased task upon the kidneys. If the products of protein metabolism be toxic, this toxicity must be exaggerated under an excessive protein diet. These considerations make it apparent that the excessive ingestion of protein might tend to alterations in metabolism and elimination that would constitute auto-intoxication. Large classes have, since time immemorial, been accustomed to an excess of protein food. We have little exact information that this has produced disease. We have no exact evidence that a moderate excess of protein is the sole and direct cause of any known disease. There are, however, individuals who under such conditions are not well, suffer from headache and insomnia, have little spontaneity and initiative, are sluggish and uncomfortable, possibly morose, and who are relieved by reduction in the protein of the diet. There is, apparently, for each person a certain excess of protein that cannot be tolerated without disturbances in the sensations of health. Excesses of protein are borne badly by infants. What is commonly regarded as auto-intoxication following the excessive use of meat is usually indigestion and not a disturbed metabolism.

Disturbances of Protein Metabolism Independent of the Input.—The retention of protein is seen only under few conditions. In youth this is of obvious purpose. Following illness, subnutrition, and starvation the body retains protein until it has returned to the normal. Under forced feeding, the body may retain protein so long as the forced feeding is maintained. There is a current idea that the metabolism of the protein is often incomplete. Following the cessation of fever in the infectious diseases, an increased elimination of urea may be observed. It is believed that during the fever the katabolic processes were incomplete and that following the defervescence they are completed and the excess of urea eliminated. This explanation, like the one defining the condition as simply a retention due to renal insufficiency, is not supported by experimental work. Even in health, the protein katabolism is subject to rather marked fluctuations.

Excess of Protein Metabolism.—This is seen particularly in six groups of sickness: fevers, infections, neoplasms, the essential anemias, exophthalmic goitre, and intoxications. As a rule, the nitrogen appears in the form of the normal end-products. Sometimes, however, intermediary products, amino-acids, appear in the urine. In some cases of acute atrophy of the liver, the nitrogen output in the urine will be very low at a time when the circulation is flooded with amino-acids; under these circumstances, these, as well as the end-products, fail of elimination.

Fever, per se, increases the disintegration of protein. The high temperature increases the cellular hydrolysis. All fermentative reactions are accelerated by increase of temperature within certain limits, and is theoretically possible that the increased combustions in simple fever are the direct result of this.

The febrile *infectious diseases*, especially of acute type, may be accompanied by very marked increases in the protein katabolism. The relations vary for different days and periods; but if the input and output for the entire course of the disease be obtained, the fact in many instances is striking. The loss is greatest during the earlier stages of the disease. Rarely is there no nitrogen deficit. As a rule, the exaggeration of the protein katabolism is more marked in the fevers than is the increase in the combustion of sugar and fat; in moderate fever the combustion of fat and sugar is often normal. The deficit may mean a loss of protein to the body, but by increasing the diet the deficit may be abolished. To accomplish this, greater quantities of sugar are necessary than would be needed in the normal subject. An increase of the ingested protein in the febrile subject is not followed by an increase in the nitrogen output to the same extent. Thus, while sugar has lost but little of its power of saving protein, protein in the diet has acquired a power of sparing protein in the metabolism—which is best explained by the assumption that there is, as in subnutrition, a protein-deficit in the circulation which the excess of ingested protein simply makes good. Heavy input of sugar is able to control the loss.

In *exophthalmic goitre* we have a striking illustration of metabolic exaggeration. Associated with an excessive or perverted functionation of the thyroid body, the protein katabolism is exaggerated. There is a deficit of nitrogen, and strenuous forced feeding (up to 60 cal. per kilo per day) may not maintain the body weight. Despite increased heat dissipation, the body temperature is normal or even increased. The exaggeration of the protein katabolism, while marked, is less extreme than the increased combustion of the carbohydrates and fats. Possibly the condition may resemble starvation; since the sugar and fats are burned in such excess their sparing power on the protein metabolism would be wanting, just as in subnutrition with a low carbohydrate ration. The thyroid body is believed to possess an internal secretion that acts as an accelerator of protoplasmic combustion; the administration of thyroid preparations or an excessive activity of the thyroid body leads to marked exaggerations in the combustions.

The exaggerations that are observed in association with the essential *anemias* are not dependent upon the *anemias per se*, but upon the con-

ditions underlying them. Simple anemia and chlorosis present a normal metabolism. In pernicious anemia and in leukemia, the protein metabolism may be for long periods notably exaggerated and accompanied by a loss of body protein. In the anemias the exaggeration of the protein metabolism is not accompanied by a notable increase in the combustion of sugar and fat. A study of these diseases has led to the assumption that they are of toxic origin, and with this the exaggeration of the protein disassimilation is in good accord.

In the *cachexia of malignant diseases* there is a notable exaggeration of the protein katabolism. It may be absent during periods of very chronic progress, but during active growth a nitrogen deficit is present, and this does not seem to be easily controlled by the ingestion of a luxurious carbohydrate ration. These cases incline also to an excessive combustion, and may indeed exhibit marked superoxidation.

Intoxications.—Poisoning with exogenous substances (phosphorus, arsenic, chloroform, and others) is accompanied by an exaggeration of the protein katabolism. As a rule, the secondary oxidations are sufficient to convert the amino-acids into the normal end-products, but in many cases these are to be found in the urine, while in the liver and blood amino-acids may be found in quantities. The combustion of sugar may be reduced during the last periods of the intoxication. The respiratory exchange has been determined to be normal. Glycogen disappears from the liver and to a large extent from the muscles. The brunt of the intoxication falls upon the protein metabolism. The excessive hydrolysis of protein is associated with exaggerated autolysis of the cells, particularly of the liver. That this postulated exaggeration of the autolysis of the liver occurs, is shown by the fact that the aseptic postmortem autolysis of the liver is much more rapid in the case of phosphorus poisoning than in the normal liver. In a word, phosphorus poisoning acts like a fermentation. Acute yellow atrophy of the liver and acute pancreatitis resemble, in their chemical details, phosphorus poisoning, and we are justified in the assumption that the acts of intoxication are similar.

The mechanisms by which these exaggerations of the protein metabolisms are carried out have not been investigated for the various conditions. The following considerations deserve mention:

Fever.—This is able to exaggerate to some degree the hydrolysis of protein.

Leukocytosis.—Associated with this is an excessive cytotoxicity, the products of which would enter the circulating plasma and be there subject to hydrolysis.

Cellular Exudates.—These, in pneumonia and septic collections, are unquestionably of great importance. During the period of resorption, the subject of a croupous pneumonia may resolve and disintegrate a kilo or more of cellular material, and in such cases the highest figures are obtained. The disintegration of such exudative collections could account for the protein deficit only during the stage of resolution, not during the stage of formation. Now since the phenomenon is present during the stage of formation, when a nitrogen retention might have

been expected, it is obvious that during that period some other active agent was in operation. The mechanism of the exaggeration of protein katabolism is here also simply that of flooding the circulation with the protoplasmic protein, which is then hydrolyzed. Closely allied is the absorption of *transudates*, whose protein is thus added to the circulation.

An important factor is the *toxic cellular degenerations*, the exaggeration of the normal autolysis. In poisoning by phloridzin, toluylene-diamine, nitro-benzol, and potassium chlorate, in addition to those previously mentioned, we find extensive and very rapid cellular degenerations.

Extreme degeneration of the liver may occur within three days of a chloroform narcosis. Similar conditions are found in acute yellow atrophy of the liver and in acute pancreatitis. These degenerated cells constitute protein excess in the circulation and are then hydrolyzed. Furthermore, there exists, particularly in the muscles, an emaciation of the cells without degeneration. That these cellular emaciations and degenerations exaggerate the protein metabolism by casting into the circulation an excess of protein is shown by the fact that it is not possible by the administration of any amount of carbohydrate to spare the nitrogenous output as much as in health.

Lastly, it is possible that there may be some direct influence on the reactions of the hydrolysis of protein, some accelerating influence of the nature of a zymo-excitor. The hypothetical substance could be derived from the metabolism of the bacteria, or less probably from the necrobiotic cells.

It is clear that an exaggeration of the protein katabolism bears no constant relation to any abnormality in the processes of carbonous combustion, and in particular one may not infer from the existence of such an exaggeration that a suboxidation is present. The failure to understand this has been responsible for much confusion.

Cystinuria.—Cystinuria is an hereditary abnormality of the protein metabolism. Cystin is derived from protein. The most obvious chemical mechanism for the formation of cystin in the body would be to assume that cystein, a normal product of protein disintegration, is oxidized to cysteinic acid, and this then converted into taurin by the splitting off of carbon dioxide, probably as a fermentative reaction. Under the pathological conditions in cystinuria, the cystein instead of being converted into taurin is converted into cystin by the union of two molecules, a sort of condensation. The administration of cholic acid to the cystinuric produces no increase in the cystinuria.

Cystinuria is usually accompanied by the excretion of pentamethylen-diamine and tetramethylen-diamine. Since these ptomains are usually found as the results of putrefaction, the first inference was that the cystinuria was of internal origin. Cystinuria has been observed unaccompanied by ptomainuria; the ptomainuria occurs in cholera and other conditions independent of cystinuria. These diamines may be recovered from the products of the tryptic or peptic digestion of protein (due to the fermentation of lysin and ornithin) but there is no reason why they may not be of metabolic derivation. Instead of terming cystinuria a condition of intestinal origin, it is better to locate the origin of the dia-

mines in the tissues. Cystinurics are deficient in the faculty of oxidizing amino-acids.

The amounts that may be eliminated are sometimes quite large, more than a gram per day. Occasionally calculi form in the kidneys or bladder. There are no symptoms of auto-intoxication and no known sequelæ except calculi. The condition is not affected by any constituents in the diet; in particular, meat does not seem to cause any noteworthy increase.

Alkaptonuria.—Idiopathic alkaptonuria is a family disease, consisting in the elimination in the urine of dioxyphenylacetic acid. It was first thought that this was formed from tyrosin in the alimentary tract and then absorbed; experimental studies are opposed to this, as is also the occurrence of the condition in the newborn infant in an alkaptonuric family. Tyrosin is formed in the intestine as an end-product of tryptic digestion. From it phenol and cresol are derived by bacterial action through a reaction of diaminization. Tyrosin is set free in the body as an intermediary product of protein metabolism. If the amount be excessive, as in extensive tissue autolyses, tyrosin appears in the urine; otherwise it is oxidized. A normal individual is able to oxidize notable amounts of tyrosin, and the abnormality in alkaptonuria consists in the inability of the body to oxidize the tyrosin derivatives beyond the stage of dioxyphenylacetic acid, which is eliminated unchanged. The inability to further oxidize dioxyphenylacetic acid is seen in occasional cases of hepatic cirrhosis, tuberculous peritonitis, and diabetes. The abnormality is unquestionably situated in the intermediary protein metabolism. This anomaly is usually the only metabolic abnormality present and the subjects are entirely well.

Uremia.—Uremia is here classed, without adequate experimental or chemical evidence, as an auto-intoxication of the protein metabolism, simply because this is the direction of least resistance. The carbonous metabolism is known to be normal. That the condition is an auto-intoxication is provisionally proved by the resemblances of the symptoms to well-known exogenous intoxications. As stated, uremia cannot be regarded as a simple retention intoxication; it is likewise not possible to incriminate any known normal constituent of the urine.

Urea.—That urea cannot be the cause of uremia is shown by its comparative innocuousness. A toxic action is obtained only by the injection of large quantities, and the withdrawal of water. The injection of urea is followed by a vasomotor dilatation of the vessels of the kidney. Animals bear such treatment without the slightest apparent result. A case has been reported in which, on the day following an eight-day anuria, nearly 150 grams of urea were eliminated. There is no parallelism between the occurrence of uremia and the urea content of the blood. There may be retention without uremia, uremia may set in without retention. There is no relation between uremia and dropsy.

Ammonia.—The theory that ammonium salts are the cause of uremia is disproved by the simple fact that no such amounts of ammonia are to be found in the blood or urine. If it were true, then in ketonic acidosis we would have uremia, since here we have the largest quantities of ammonia in the blood and urine, and it would be immaterial for the

causation of an intoxication whether the ammonia were withdrawn from the urea metabolism to be combined with the fatty acids, or originated in a fermentative decomposition of urea or in its non-formation. Uremia cannot be produced by the injection of salts of ammonia.

Creatinin and Creatin.—The extractives are not responsible for uremia. They are not retained prior to the attack. In animals under ether anesthesia, the application of creatinin to the exposed cortex causes spasms and convulsions, but since these may be provoked by innumerable substances, the conclusion that creatinin is the poison in uremia is unwarranted. Creatinin and creatin are not increased in the urine or blood during uremia.

Rest-nitrogen.—This fraction, most largely retained in nephritis, cannot be regarded as the cause of uremia.

The Salts.—Equally unsatisfactory is the theory that the toxic agents lie in the salts, particularly of potassium. If the salts be injected slowly and not in hypertonic solution, the tissues will accommodate themselves to very large quantities. Now in nephritis the accumulation is slow and hypertonicity is never produced. The more recent studies of the actions of salts have given no support to the saline theory of uremia. The injections of hypertonic solutions will not provoke uremia in nephrectomized animals.

We are thus led to the conclusion that the causation of uremia is to be sought neither in the retention of the total urinary secretion nor in the retention and toxic action of any known constituent. Consequently, since the end-products of protein metabolism cannot be held responsible, we may look for the agent in the intermediary metabolism. Three possibilities suggest themselves:

(a) The functions of the kidney include an act of katabolism in which some intermediary product is converted into an end-product; in nephritis this function would be to a certain extent non-operative and an intoxication would result. This avoids entirely the difficulty of explaining why no intoxication is produced in the functional anuria. Studies in fractional extirpation of kidney substance lend support to this view.

(b) A metabolic anomaly lies behind the kidney, associated with the renal lesions as cause, effect, or correlation. This is a hypothetical proposition; we possess, however, a suggestive analogy. The intoxication that sometimes follows the switching of the liver out of the circulation is in many respects like uremia. If the hepatic artery be ligated, death occurs within a few hours under most excessive acidosis for which the available ammonia is insufficient. The loss of the hepatic circulation entrains greater disturbance of metabolism and intoxication than does the loss of the portal circulation, with its concomitant approximate abolition of the formation of urea.

(c) The kidneys possess an internal secretion necessary for the intermediary protein metabolism, the absence of which is followed by metabolic disturbances ending in intoxication. This theory avoids the difficulty of explaining the non-occurrence of uremia following prolonged total retention; it is not irreconcilable with the observations that in some diseases, like pernicious anemia, no uremic symptoms appear,

although the kidneys present extensive degenerations, while, on the other hand, uremia may appear in some renal intoxications, as in cantharides poisoning, that are accompanied by only moderate lesions.

Conceding that we possess as yet no qualitative demonstration of the theory that the cause of uremia lies in the intermediary protein metabolism, are there quantitative variations? It is known that peculiar fluctuations in the nitrogen occur in nephritis; periods of retention are followed by periods of deficit, and these without any regular relation to the dropsy or to the symptoms of uremia. No one can work with the nitrogen metabolism of nephritis without being convinced that there is something wrong which is not expressed in the end results except in an incidental manner. The influence of various diets on the metabolism of nephritis is not known; we have only superficial studies on the relations of different diets to albuminuria. The albuminuria is of no metabolic consequence to a nephritic who has moderate powers of digestion. An excess of uric acid is often found in the blood in nephritis, but normal values are obtained in the urine. Acidosis is not present in uremia, nor is the urinary elimination of ammonia particularly high.

The retention of normal end-products, to summarize, cannot be regarded as the cause of uremia. As before stated, it may be related to nephritic hypertension. The hypothesis that hypertension is due to excessive action of epinephrin has failed of demonstration.

Overexertion.—There is a condition termed autotypyphization, apparently of autotoxic origin, resembling the *surmenage* of animals, seen following prolonged and abnormally heavy exertion. Unlike the *surmenage* of animals, it seems to have no relations to the diet. The symptoms are fever of irregular type, headache, muscular prostration, albuminuria, sometimes an elimination of lactic acid, probably a slight excess in the nitrogen elimination, and often cardiac dilatation. Possibly the conditions that have been described in foot-ball players following severe games are related to *surmenage*.

AUTO-INTOXICATION ASSOCIATED WITH THE PURIN METABOLISM

Concerned in this metabolism are the substances derived from the purin nucleus: uric acid; several bases, xanthin, hypoxanthin, adenine, guanine; and three vegetable bases, caffeine, theobromine, and theophyllin, all methyl-xanthins. The purin input consists of nucleins and preformed purin bodies contained in the diet, and the bases contained in tea, coffee, and cocoa. The purin input varies with the diet, from nothing to 15 grains (1 gm.) per day. The nuclein is hydrolyzed in the alimentary tract and split into purin bases, pyrimidins, a pentose and phosphoric acid; the purins thus derived join, in their absorption, the preformed purin of the diet. Purins are in part oxidized or destroyed in the intestinal tract. After absorption the purin may be oxidized or eliminated unchanged. Ingested uric acid is eliminated in part unchanged, in part as urea; xanthin, hypoxanthin, and adenine are eliminated in part

unchanged, in part as uric acid; the methyl-purins are eliminated as methyl-xanthin, not oxidized to uric acid. In a certain sense, therefore, all these bodies may be termed intermediary products. Obviously therefore the purin output on an ordinary diet comprises an exogenous and an endogenous fraction. For the purposes of clinical experimentation the exogenous purin may be excluded by the employment of a diet of milk, eggs, sugar, and starch.

Is the purin output derived solely from the input and nuclein katabolism or is uric acid formed by synthesis? In other words, does the endogenous purin proceed entirely from the nucleinic metabolism, or is purin otherwise formed? Hypoxanthin is formed during the period of exercise of muscle, an important observation whose bearing on the practical problems is not yet definable. Purin may be derived from purin and nuclein in the diet, and from the katabolism of nuclein; purin bases may be eliminated as derived from each of these sources; they may also be converted into uric acid. Uric acid may be derived from the purin and nuclein input and from the nuclein katabolism; uric acid may be eliminated as derived from these sources and may also be converted into urea.

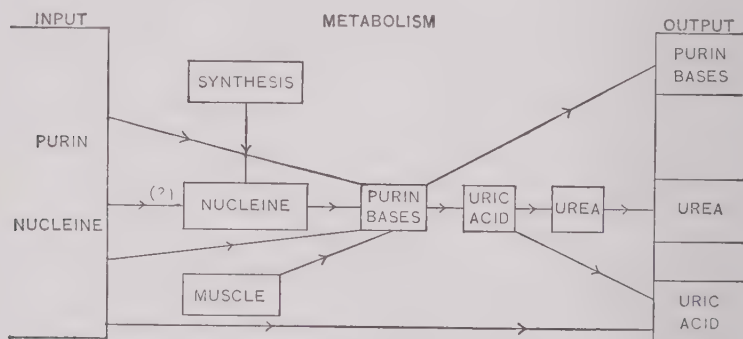
There is no parallelism between leukocytosis and uric-acid output. The circulating leukocytes are but a fraction of the total leukocytes, and the assumption of a regular cytolytic proportional to the total increase is unfounded. In pneumonia the uric-acid output is parallel with the resorption of the exudate, not with the circulating leukocytes. The excess of uric acid in dogs with an Eck fistula, following cauterization of the liver, and in acute yellow atrophy of the liver and phosphorus poisoning, cannot be related to the lymphatic system. Leukocytosis and an increased output of uric acid are correlated results of a common cause, but the latter can occur without the former. The purin metabolism is concerned with the nuclein of the entire body and not specifically with that of the lymphatic system.

Is the purin absorbed from the alimentary tract utilized for the synthesis of nuclein? In health the intensity of the purin metabolism is quite constant. If the ingested purin be utilized in the synthesis of nucleinic acid, less would be required from other sources. That the body can easily synthesize purin directly is shown by the formation of nucleic acid in the hatching chick, by the regular functioning of the purin output on a milk diet, and by experiments on growing animals. If now exogenous purin be utilized in the synthesis of nuclein, the exogenous purin of a particular diet cannot be subtracted from the total purin output in order to arrive at a figure for the purin output of endogenous origin. Since the increase of a purin input is followed by an increase in the output, it follows either that the purin metabolism behaves like the common protein metabolism—an excess of the substrate results in an acceleration of the katabolism—or else the absorbed excess is simply eliminated directly. The present evidence indicates that exogenous purin is not utilized in the synthesis of nuclein; the purin and pyrimidin rings are synthesized *de novo* from protein, the pentose from hexose, and these then combined with phosphoric acid to form the nucleic

acid. In all probability the purin metabolism, through it concerns a group of structures, is subject to exaggerations whenever abnormal excesses of cytolysis occur.

The seat of the oxidation of purin bases to uric acid is not single, although the liver is particularly active in this function. Birds and dogs when deprived of liver are still able to secrete uric acid. That the lymphatic structures have the power of effecting this oxidation has been experimentally shown. The older theory that the kidneys were the chief seat of this oxidation is now discredited. This reaction is to be regarded as a fermentative oxidation. The synthesis of uric acid occurs in birds only in the liver. The oxidation of uric acid to urea has not been brought into definite connection with any organ. The liver, kidney, and muscle of the dog and pig have the power of thus oxidizing uric acid. The oxidation of uric acid to urea is probably not a pronounced phenomenon. It is certain that the purin output represents the larger part of the purin metabolism, *i. e.*, an end rather than an intermediary product.

Now these facts, apart from the light they may throw upon this complex problem, demonstrate one point of practical importance in the interpretation of urinary analysis. Without the purin input being known the estimation of the uric-acid excretion is worth nothing as evidence of the state of the purin metabolism. But even with the purin input known (or excluded), the estimation of the uric acid alone, or of the total purin, cannot be used to determine whether the purin output be normal, increased, or decreased, the purin metabolism normal or abnormal. The diagram illustrates the facts of the purin input, metabolism, and output.



It is apparent that by no estimation of the output of uric acid or the total purin can a conclusion be drawn of the magnitude of nuclein metabolism, unless we control the other variables, which we are not able to do.

There is no constant relation between the purin and protein metabolisms or between the purin output and the urea or nitrogen output. It is possible by an arbitrary modification of the diet with respect to the ingestion of common protein and nucleic tissue to vary the ratio

within very wide limits; the urea uric-acid ratio gives no information of either metabolism, it is a dietary index solely. While a certain amount of purin may be converted into urea, the amount of nitrogen concerned is too small to affect the total nitrogen. The purin metabolism is, however, not entirely independent of the general metabolism. In starvation the purin output is not reduced corresponding to the reduction in the urea. The nucleic metabolism is an integral part of the daily life of the cellular nuclei; it is not notably reduced in starvation or replaceable by any other metabolism, and has no role in the caloric or energetic aspect of general metabolism. The purin output may be increased by heavy protein intake.

Exceedingly important are the questions that relate to the form in which the uric acid circulates in the blood, its solubility, and the influence of the reaction of the blood upon these relations. Uric acid circulates only in the form of the monosodium urate. Uric acid is soluble in water 1 part to 40,000. Monosodium urate is soluble in water 1 part in 1800. The blood serum may contain normally 1 to 3 milligrams of uric acid in 100 cc. Abnormal amounts have been determined to exist in most cases of acute gout, in many cases of nephritis, arteriosclerosis, pneumonia in the stage of resorption, in conditions associated with the disintegration of cellular exudates, following a meal rich in nuclein, and most markedly in leukemia up to 10 to 15 or even 25 mgs. in 100 cc. of blood. Whenever an increased blood-content is accompanied by an increased output, it may be reasonably inferred that an exaggerated nuclein metabolism or purin input exists. Whenever an increased content is not accompanied by an increased output, as in gout and nephritis, there remain two possibilities—if one assumes that the chemical form in which the uric acid circulates is the same as in the normal—a decreased oxidation of uric acid or a retention through failure of renal elimination.

As regards *gout*, there is no evidence that the gouty individual displays any abnormality in the assimilation of purin; the ingested purin is quantitatively absorbed from the digestive tract, as shown by the nitrogen balance and by the elimination of phosphoric acid. In some diet experiments the elimination of purin following the ingestion of sweetbreads was normal; in others there seemed to be a retention, the phosphoric acid was eliminated but not the purin. In gout a retardation in purin katabolism may often be demonstrated.

Does the uric acid in the blood in gout circulate in the same form as normally? We have no data tending to show that the solubility of uric acid in the blood is decreased in gout. There is some evidence that the uric acid in the blood in leukemia circulates in part in a form different from the normal.

Is there a diminished power of elimination of uric acid *per se* in gout? When we recall that from the purin output alone, even with a controlled purin input, the magnitude of the nuclein metabolism cannot be estimated, we realize that a retention cannot be thus determined. Conceding that many cases of gout have renal lesions and that many cases of renal sclerosis have urate depositions, it is still not possible to maintain that the excess of uric acid in the blood is the simple result of retention

due to renal disease. The fact that the gouty kidney can eliminate an excess of uric acid after the ingestion of thymus, though delayed in time, argues neither for nor against the theory, since a diseased organ may respond to extraordinary stimuli. On the contrary, the fact that in chronic nephritis the ingestion of thymus is followed by an increase in the blood-content as well as in the elimination, does not prove that the fault lies in the kidney. The renal theory of gout can be assumed only by postulating an elective type of purin nephritis. In chronic gout and in the intervals between the attacks in acute cases, the purin output is normal. Prior to the onset of an acute attack of gout there is a diminution in the uric-acid output, followed by an increase; it has not been shown that this bears constant relations to variations in the blood-content of uric acid. It is scarcely possible to believe that the attack is dependent upon the diminution in the output; the quantities concerned are too small to be the direct etiological factor. The depositions cut no figure in the quantitative relation; whether the urate depositions are ever absorbed with such rapidity and to such an extent as to show in the output is doubtful.

The deposition of urates is not the direct result of an excess of uric acid in the blood; they are absent in conditions other than gout, particularly leukemia, in which an excess is present in the blood. Nor is the deposition to be explained by the coincidental occurrence of an excess of uric acid in the blood and a lesion in the tissues. Gout would be very easy of experimental production if nothing but an excess of uric acid in the blood and a local lesion were required. The formation of tophi must rest upon some physicochemical basis of precipitation and crystallization. The cartilage is rich in sodium, and preponderance of sodium tends to precipitate monosodium urate. That necrosis cannot be the sole substratum is certain.

These various facts compel us to assume that the actual etiology lies deeper than quantitative variations in the uric acid; the determining moment lies earlier in the purin metabolism. That these earlier factors may have relations to retention is not denied, but the retention is a result and not in itself an etiological factor. In a certain sense, the uric acid must be considered as the innocent weapon of the disease. The idea that the uric acid is itself the toxic agent, that it by a local action as uric acid inaugurates the local lesion, or that the local lesion is simply the reaction of the tissue to a crystallization of uric acid as a physicochemical fact is contrary to our best knowledge. That the purin bases are devoid of that marked toxicity that was some time ago ascribed to them is now known; they are not in gout increased at the expense of the uric acid. The actual act or defects in metabolism associated with the depositions in gout and the symptoms of the disease are at present wholly unknown.

Oxaluria.—There is no relation between the amount of oxalic acid in the urine and the quantity of crystals of calcium oxalate in the urinary sediment. Oxalic acid is formed in the normal body in the entire absence of the acid from the diet. Of the oxalic acid contained in the diet the larger part is destroyed in the alimentary tract. In all probability oxalic

acid is not oxidized in the body. Oxaluria is no more common in the gouty than in others, and there is no clinical evidence of any relationship between oxaluria and disturbances of the purin metabolism.

Insofar as the common protein metabolism is concerned, oxalic acid is formed from gelatin and creatin; it is experimentally not to be derived from any excess of fat or carbohydrate in the diet. There is no experimental evidence that it is, in the body, derived from glycuronic acid or bears any relation to it. Oxalic acid is likewise easily obtained from the higher fatty acids, but there is no evidence that it is in any way associated with the normal fat metabolism or the abnormal ketonic acidosis. Lastly, oxalic acid might be derived from the oxidation of oxy-acids such as lactic acid. In this manner it might be derived from sugar.

It is apparent that these facts shed no light upon the traditional symptom-complex of oxaluria. That this symptom-complex possesses anything but a definite objective character is freely admitted. In any event there is no reason to incriminate the oxalic acid. In the quantities concerned it is innocuous and the symptoms currently attributed to the condition bear no resemblance to oxalic acid poisoning. That calculi form is a chemical accident.

AUTO-INTOXICATION ASSOCIATED WITH THE CARBOHYDRATE METABOLISM

The digestion of the starches and the higher sugars is an act of hydrolysis. Ordinarily all the sugar absorbed (apart from pentoses) is in the form of hexose. It is possible under normal circumstances for higher sugars to be absorbed unchanged; the power of the alimentary tract to invert disaccharides is limited. This mellituria is a strictly alimentary type; the sugar appears in the urine unchanged. In the common form of alimentary mellituria, the sugar in the urine is glucose. Normally no mellituria follows the ingestion of starch; time is the controlling factor in alimentary mellituria; if absorption be heavy in the unit of time, it will produce hyperglycemia. The normal individual will not exhibit mellituria following the ingestion of 5 ozs. (150 gms.) of glucose or levulose or nearly double that amount of saccharose or maltose; milk sugar is often less well tolerated.

The absorbed sugars are converted into glycogen, but not all hexoses with equal readiness. It is not definitely known whether the different hexoses that are formed in the digestion of sugar (d-glucose, d-levulose, and d-galactose) are absorbed unchanged or whether they are converted into d-glucose during the passage through the intestinal mucosa. In the event of their absorption unchanged they must be converted into d-glucose in the liver. According to our present evidence d-glucose is the combustion form of sugar; it is this hexose alone that is formed from glycogen, and the body unquestionably possesses the power directly, and probably indirectly, of converting the different hexoses into d-glucose. This is of practical importance, since it explains why the use of galactose

or fructose is rarely of benefit to the diabetic; instead of burning the sugars directly, the body converts them into d-glucose. That the body cannot only form d-glucose from d-galactose, but also form the latter from the former, is shown by the synthesis of d-galactose in the central nervous system and in the breast glands. Alimentary levulosuria is a sign of organic liver disease.

Following the conversion of glycogen into glucose, the latter is utilized in combustion for the maintenance of the body temperature and the formation of fat. The reactions of the combustion of glucose are not definitely known. Experimental work has made it probable that the combustion of sugar in the body follows in a general manner the following scheme: glucose \rightarrow methyl glyoxal \rightarrow lactic acid \rightarrow ethyl alcohol \rightarrow acetic acid \rightarrow carbon dioxide and water, carbon dioxide being set free also with the appearance of alcohol, water being evolved with the appearance of acetic acid. The particular importance of this scheme of oxidation lies in the fact that it makes ethyl alcohol a normal intermediary product in the sugar metabolism. The combustion of sugar is an act of fermentation. For the maximum acceleration of the reaction, substances derived from two sources are necessary—the muscles and the pancreas.

We may regard the muscular enzyme as primary, and the pancreatic substance (that seems to be associated with the integrity of the islands of Langerhans) as a zymo-excitor. It has not been proved that this relation is the sole one associated with the burning of sugar in the body, nor is the loss of the power of burning sugar always associated with lesions in the pancreas. The process by which fats are formed out of sugar is not known. However this conversion is effected, the function is directly associated with the katabolic power of the carbohydrate metabolism, just as is the formation of glycogen.

Normally the body sugar is derived from the carbohydrates of the diet and from protein. A fraction of the amino-acids resulting from the hydrolysis of protein (apparently all such as are converted into propionic acid) is converted into glucose. In quantity this means about 4 grams of sugar to 1 gram of protein nitrogen.

The limit of assimilation of cane-sugar is some 200 grams; it is obvious that were an individual to supply his whole heat by the use of sugar, he would at each meal approach the limit of assimilation. This may be avoided by the substitution of starch for sugar, and such a ration is adequate to the greatest physical exertion. If more carbohydrate be ingested than is necessary for the maintenance of the body heat, the remainder is converted into fat. The combustion of carbohydrate is determined not by the input but by the demands for heat and energy.

Important for the estimation of the carbohydrate metabolism is a reduction of the limit of assimilation. This may be lowered to less than one-half the normal with no signs of ill-health. This reduction is usually confined to glucose and saccharose, not to levulose and lactose. An alimentary mellituria associated with a starch diet is always pathological. The best interpretation of the reduction of the limit of assimilation is that the power of the liver to convert a unit of sugar into glycogen in the unit of time is reduced. A lowering of the limit of assimilation is

regularly seen in exophthalmic goitre and often in alcoholism, gout, arteriosclerosis, lead poisoning, organic diseases of the liver, obesity, and in some of the psychoses and organic diseases of the nervous system. A susceptibility to levulose has been observed in cases of hepatic disease, and constitutes a sign of advanced hepatic disease. The condition may be mild or pronounced and may be associated with a reduction in the power to burn sugar, but is in itself not associated with hyperglycemia, apart from the period following the ingestion of the sugar.

Superoxidation.—Excessive combustion of sugar is a common phenomenon. Most prominent in Graves' disease, it is seen also in infectious diseases, in severe anemia, in malignant neoplasms, and in cachexia due to other causes. It is usually not marked in the febrile infectious diseases; the supercombustion is less marked than the exaggeration of protein katabolism. Though such a superoxidation of sugar usually accompanies fever, it does not in itself produce fever. The excess of combustion has apparently two causes: an exaggeration in the fermentative acceleration and the lowering in the saving power of sugar for protein. The excessive combustion of sugar is in itself unattended with any untoward results, the body seems able to carry the process to the end-products; that the body may not be able to control the heat dissipation can be no fault of the carbohydrate metabolism.

Suboxidation.—A lessened combustion of sugar as a quantitative abnormality is, apart from acute conditions, such as shock, hemorrhage, etc., probably met with only in true diabetes. In no other condition is there evidence that the body burns fat or protein to maintain the heat as the consequence of an inability to burn sugar. Since the combustion of sugar is a fermentation, the only dynamic explanation for the loss of the faculty, since the concentration of the sugar is not lowered, is to assume the loss of the ferment or of some zymo-excitor, or the presence of some condition inimical to the action of the ferment.

Glycosuria.—Glycosuria may be associated with normal or hyperglycemia. An increase of sugar in the blood may be due to an increased formation or a decreased oxidation. Glycosuria with a normal blood-content is probably associated with some abnormality in the renal functions. We have evidence that all these forms exist clinically. That of the number of non-diabetic glycosurias some are best explained as results of renal disturbances is certain. Glycosuria due to an increased formation of sugar may be due either to an excessive input, to an inability of the body to convert the absorbed sugar into glycogen, or to what might be termed an instability in the storage of glycogen. Glycosuria *per se* need have no consequence to the metabolism.

Diabetes.—In diabetes are concerned several disturbances of intermediary metabolism: loss of the power of burning sugar; loss of the power in the liver and muscles of converting sugar into glycogen; loss of the power of converting sugar into fat; loss of the power of burning fat completely and in the normal manner. The loss of the function of oxidizing sugar is a gradient in which the successive lapses may be grouped about as follows, in the order of their severity: The loss of the power of assimilating starch—mellituria after starch

ingestion; reduction in the limit of assimilation of sugar to the point when any sugar causes a glycosuria; reduction in the assimilation of starch to the point when any starch is followed by glycosuria; the partial loss of the power of burning sugar; the loss of the power of burning sugar during exercise; the loss of the power of burning more sugar during fever; the loss of the saving power of carbohydrates on the protein metabolism; and the total loss of all power of burning sugar. The last is extremely rare. The succession of losses in function does not necessarily occur in the order given and a function once lost may be regained. In proportion to the loss in the power to burn sugar, the heat of the body must be maintained by the combustion of protein and fat. The inability to convert sugar into glycogen is rarely lost, the tissues are not devoid of glycogen. The power of prompt conversion of alimentary sugar is often lost. The power of forming fats from sugar is reduced, in severe instances entirely absent.

The origin of the excessive glycemia is a fundamental problem in diabetes. It is now generally held that the quantities of sugar eliminated in severe diabetes on a carbohydrate-free diet cannot be explained on the basis of the preformed glycogen and glycosides. The sugar must be derived from the protein or the fat. Under fat is understood fatty acid; though glycerol can be converted into fat, the available quantity is too low to make it of moment. Within recent years the views with reference to the formation of sugar from protein have undergone a change. Formerly it was assumed that protein was separated into a nitrogenous and non-nitrogenous moiety; from the latter the glycogen was derived directly. Recent studies have shown that the end-products of protein katabolism are amino-acids, and that the carbon as well as the nitrogen of the protein is to be found in these products. Consequently, the formation of sugar from protein means the formation of sugar from amino-acids. The experimental formation of sugar from amino-acids is definitely proved; 1 gm. of protein will yield about $\frac{1}{2}$ gram of glucose. It is also certain in natural diabetes that glucose is formed from the protein katabolism and proportional thereto. There is no proof that sugar is formed from fat in the normal or diabetic organism.

Superoxidation occurs in diabetes. The carbonous metabolism is always unbalanced. The respiratory quotient is very low and is not raised by the ingestion of carbohydrate. With good powers of digestion it is usually possible to obtain a nitrogen balance, except in the periods of deterioration. It requires much more protein than normal to accomplish this and this greater amount of protein is directly proportional to the gravity of the case. For this condition, which is an important practical one, we have first the explanation that fat does not equal sugar in its power of sparing protein. But only in the mild cases is this explanation sufficient; a diabetic will commonly have a nitrogen deficit on a diet of fat and protein such as would fully suffice for a normal individual. This is to be explained on the ground that the diabetic does not utilize the sugar formed from protein. In diabetic coma the nitrogen deficit is most marked, so marked that an additional explanation is usually sought in a toxic exaggeration of the protein katabolism.

To what the toxic symptoms of diabetes are due is known only in part. In all probability the intoxications come rather from the perverted protein and fat metabolism than from the suboxidation of sugar. The coma is an acidosis, due to the perversion of the fat katabolism. While there is no direct evidence that hyperglycemia *per se* exerts a toxic action, the fact remains that the general condition of the diabetic is made worse and his power of burning sugar still further reduced by the ingestion of carbohydrate, while the maintenance of a strict diet with retention of a fair power of burning fat will ameliorate the symptoms and tend to a recovery of the power of burning sugar. Some of the toxic symptoms, as the disturbances in nutrition of tissues, are not related to the acidosis, the toxicity of the ketone bodies or to the hyperglycemia, but seem to rest upon some deeper abnormality in the protein metabolism.

There is now a large experimental literature bearing upon the relation of ductless glands to the carbohydrate metabolism. Thus extirpation of the hypophysis cerebri results in increase in carbohydrate toleration, while in some clinical cases hypertrophy of this tissue has been associated with reduced tolerance. Experimentally, the thyroid and adrenal bodies influence the relation of the pancreas to carbohydrate utilization.

AUTO-INTOXICATION ASSOCIATED WITH THE FAT METABOLISM

The digestion of fat is an act of simple hydrolysis, the fats being split into the fatty acids and glycerol. Fat is carried in the circulation partly in emulsion, favored by the colloidal nature of the blood plasma, but largely in solution. The fat in solution in the blood is dialyzable and apparently enters the cells in that form, there to be in part reconverted into insoluble fat. We may assume that the fat is utilized in the metabolism in this soluble state. The process of formation of fat from sugar is not known. Fat is the most potential form of carbonous food and is able to supply the entire caloric demands of the body. Nevertheless fats do not equal carbohydrates in the power of saving protein.

A trace of acetone is present in normal urine, derived from the reduction of diacetic acid. Whenever the fat katabolism is exaggerated, the acetone is increased and diacetic and β -oxybutyric acids may appear. We believe that these substances are normal intermediary products in the fat combustion. Acetone itself is not oxidized in the body. It is derived from aceto-acetic acid by reduction, carbon dioxide being split off. The diacetic acid is derived from β -oxybutyric acid by oxidation. The normal trace of acetone is increased in every condition accompanied by an exaggeration in the combustion of fat. Normally β -oxybutyric and diacetic acids, when ingested, are oxidized; no appreciable reduction of the diacetic acid to acetone occurs. When fatty acids (with an even number of carbons) are burned in the animal body, the beta carbon is the point of oxidation. Therefore all higher fatty acids (of even carbons) must finally, on progressive oxidation, reach the stage of butyric acid. This is then converted into β -oxybutyric acid, diacetic acid, and burned as such, traces of the latter being reduced to acetone. In diabetes the body is unable to oxidize the β -oxybutyric and diacetic acids.

Suboxidation.—Of a suboxidation of fat we have no knowledge. There is no call for any oxidation of body-fat so long as the sugar and protein of the diet are sufficient to the caloric needs of the body.

Superoxidation.—A superoxidation of fat occurs under all circumstances associated with a superoxidation of sugar if the sugar of the diet be insufficient. Except in Graves' disease and rapidly advancing malignant neoplasms, it is usually possible, if the powers of digestion are normal, to administer such an amount of sugar and fat as to leave the body-fat intact. The greatest exaggeration of the fat katabolism is seen in diabetes. Here it is associated with an excessive utilization of protein. It is often impossible in a diabetic by the administration of fat to hold the katabolism to the level of the normal. More fat is furthermore utilized than is apparent in the respiratory exchange.

Superoxidation of fat is always associated with the appearance of the ketone bodies in the urine. This supports the theory that these acids are normal intermediary products in the fat katabolism. Their appearance indicates either some limit to their oxidation or an abnormality in the last stages of the reactions. The formation of the acetone substances bears no known constant relation to the total combustion of fat; apparently it represents but a small fraction, the larger part proceeding to the natural end-products. In grave terminal diabetic coma, however, but little of the fat combustion reaches the final stage (1 mol. fat = 1 mol. β -oxybutyric acid). This of course does not furnish enough heat, and is one reason why the protein katabolism is so exaggerated in these comas, since it is then the only metabolism that can furnish heat for the body.

The Ketone Complex.—Under this term we group the associated elimination of acetone, diacetic acid, and β -oxybutyric acids in the urine. The term acetone complex was coined to differentiate the condition from the acidosis due to other acids. Except in the last stages of diabetic coma, the acids circulate and are eliminated as salts. The ketone bodies are derived from the fats and not from the carbohydrates or protein. Clinically, in all the different groups of the acetone complex, when the condition is severe the acids accompany the acetone, and this speaks directly against the origin of the acetone from the protein katabolism.

The current conception of the acetone complex connects with its disturbances in the carbohydrate metabolism in the sense that a reduction of the carbohydrate combustion comprises the essential condition for the elimination of acetone, diacetic, and β -oxybutyric acids, the oxidation of the higher fatty acids of carbon dioxide and water being only then completed when a certain amount of carbohydrate is simultaneously burned. There are instances of ketonuria in which this does not seem to hold. There are instances of the acetone complex in which there are no signs to indicate any disturbance in the carbohydrate metabolism, or indeed any exaggeration in fat combustion. Cases occur in which we have no evidence that the protein, carbohydrate, or fat metabolism exhibit any quantitative variations, and only the fat metabolism displays this qualitative variation. Acidosis is very easily developed in childhood and often to an exaggerated degree with trivial illness.

Acetone Complex Associated with a Low Carbohydrate Combustion.—*Starvation.*—A few days after the withdrawal of food the acetone group appears in the urine. When the stored glycogen is burned up, the heat must be derived from protein and fat, and since the nitrogen output is restricted, the bulk of the heating falls to the burning of the fats. A pure protein diet or a protein-fat diet has the same result.

In *febrile diseases* the complex is common. The fever makes large demands on the carbohydrate metabolism, the hepatic glycogen disappears, and, as the input is under these circumstances usually diminished, an exaggerated burden falls on the combustion of fats. β -oxybutyric acid is rare in the febrile acetonuria; diacetic acid is often present. In *diabetes* the body seems to have lost in large part the normal power of burning diacetic and β -oxybutyric acids. In diabetes, as in the two previous conditions, the administration of sugar will lower the output of the acetone substances. In severe cases the administration of sugar will not lower the output of the acetone substances.

Instances of Acetone Complex in Which there is no Evidence that the Carbohydrate Metabolism is Deranged.—In the cachexia of carcinoma, in severe infections, in atrophy of the gastric mucosa, in severe cases of anemia accompanied by a rapid loss of flesh, we may encounter the acetone complex. It is rarely marked; β -oxybutyric acid is usually absent, and diacetic acid is not always present. In these cases the individuals are ingesting carbohydrate, there is no mellituria, there are no signs that the carbohydrate metabolism is exaggerated or depressed, there is nothing to indicate that there is in the body either a diminution of the glycogen or a loss of the power to convert it into sugar, to burn sugar, or convert it into fat.

Instances of the Acetone Complex without Quantitative Alterations in any Metabolism, with Normal Qualitative Protein and Carbohydrate Metabolism.—Here are to be classed those seizures associated with marked gastro-intestinal symptoms. The subjects are usually in good health, the onset is sudden, the symptoms of irritation of the alimentary tract are marked. There is pronounced urinary acidosis; grave nervous symptoms may supervene, even death. Most of them yield promptly on lavage of the stomach and colon, free purgation, and symptomatic treatment. Many resemble exactly toxic gastro-enteritis, but others are obviously something more. Here also must be grouped the cases of recurrent vomiting in children associated with this complex. There are in these no symptoms of gastro-intestinal lesion; the vomiting is reflex in all likelihood. Probably related are the cases of convulsive pseudo-epileptic seizures associated with acetonuria. These subjects are all on ordinary mixed diet, have no glycosuria or albuminuria, and usually recover under symptomatic treatment. The administration of sugar does not affect the acetonuria. That they are ever of gastro-intestinal origin, in the sense that the acetone bodies are formed in the alimentary tract and then absorbed, is entirely without evidence. The only logical explanation, if one inclines to a gastro-intestinal etiology, is to assume that a hypothetical gastro-intestinal intoxication inaugurates secondarily a perversion of the intermediary fat metabolism.

Instances of Acetone Complex Associated with Disturbances in the Protein Metabolism.—There are now quite a number of cases reported in which following anesthesia the patients suddenly pass into a state of intoxication, often with jaundice, ketonic acidosis, the elimination of leucin and tryosin in the urine, coma, and death, with the finding of extensive degeneration of the liver at autopsy. In many cases following operations, particularly in children, a transient acetonuria occurs without dangerous symptoms or signs of abnormality in the carbohydrate metabolism.

An interesting group of conditions in which the acetone complex may occur is seen in diverse exogenous intoxications. It is not possible to believe in advance that these poisons act alike in this regard, nor can it be urged that they bring about a cessation or reduction of the carbohydrate metabolism. Very interesting is the acetonuria commonly seen on withdrawing morphine from an habitué; if the drug be resumed the complex disappears. The logical interpretation is that the incompleteness in the fat combustion resulting in the acetone complex may be brought about by several causes.

Mode of Action of Intoxication in the Acetone Complex.—The mode of intoxication may be referable to the substances themselves or to their behavior as acids. The term acidosis expresses the view that in their behavior as acids lies the chief harm. Acetone is but slightly toxic. The salts of diacetic and β -oxybutyric acid have some toxicity, which is probably greater in the diabetic because of the inability to oxidize them. When one considers the really enormous quantities of the substances that may be voided in a day, one must hesitate to say that there can be no direct intoxication from them. The general interpretation is that these acids act by withdrawal of cations. How this leads to a secondary intoxication is not known, but it does so in experimental acid intoxication. The carbon dioxide of the blood in diabetic coma has been found reduced to less than one-half the normal. The reaction of the blood remains normal. It is likely that reduction in the carbon dioxide of the blood may indirectly disrupt equilibria in the tissues of great importance to function. The sudden onset of symptoms in the acute cases can scarcely be explained on the ground of simple acidosis, yet alkali treatment is here most effective. It is a noteworthy fact that the injection of sodium bicarbonate is followed, as a rule, by recovery in the non-diabetic cases, as an exception in diabetes—although this does not in itself antagonize the contention that the intoxication is simply an acidosis.

The study of hormones indicates a possible *modus operandi* of auto-intoxication. Assuming that there is between the liver, pancreas, adrenal thyroid, and hypothesis a chain of connection of hormones, it may be possible that the function of one organ in metabolism might be diverted through disease in a different organ. And as a chain is no stronger than its weakest link so the chain of interaction of hormones may fail entirely when the internal secretion of one organ is disturbed. From this point of view, it is clear that auto-intoxication might represent complex deviations, not directly connected with the particular metabolism through which it is clinically manifested.

PART V

DISEASES OF METABOLISM

CHAPTER XVI

GENERAL CONSIDERATION OF METABOLISM

BY PHILIP B. HAWK, M.S., PH.D.¹

Introduction.—We may define metabolism as *all chemical and physical changes which occur in living matter and which constitute the basis of the material phenomena of life*. This definition holds for the chemical and physical transformations of the simplest organisms as well as for those of the highest degree of complexity. This conception of metabolism is broad enough to include the simple metabolic processes of the individual cell, such as the amoeba, or the intricate metabolic processes of the human organism. We may differentiate between two distinct forms of metabolism which are characterized respectively as *anabolism* and *katabolism*. In anabolism we have to do with *constructive metabolism*, the synthetic transformation of simple molecules into more complex ones. In katabolism we are concerned with *destructive metabolism*, the analytic changes by which complex molecules yield simpler ones.

Through the medium of the anabolic processes, the end-products resulting from the transformation of the various foodstuffs after being transported to the cells of the different tissues are there in part built up by synthetic processes into the cell structure or stored as a reserve supply for future use: a further portion remains in circulation in the blood and lymph. Through the medium of the katabolic processes the material mentioned above as either being in circulation, or stored as a reserve or as forming an integral part of the living cellular substance, is reduced by analytical cleavage processes, and the simple fragments, after yielding the major portion of their energy in the form of heat or mechanical work, are eliminated from the body. Bearing these facts in mind we see that the chemical side of metabolism is closely associated with the physical side. For each chemical change there is a corresponding physical change. Metabolism of matter is therefore accompanied by metabolism of energy. For example, when the changes are anabolic

¹ The section in the previous edition was written by Russell H. Chittenden and Lafayette B. Mendel, of Yale University. It has been revised, portions rewritten, and new matter added.

in character there is a change from kinetic to potential energy. In other words, constructive metabolism is associated with a storage of energy. When the katabolic forces are in play the potential energy becomes kinetic through the cleavage or oxidation of the complex molecules of the living cellular matter. This constitutes what we may term *physical katabolism* as distinct from *chemical katabolism*.

All the varied chemical changes which take place in the animal organism during the course of the complicated metabolic cycle obey the law of the conservation of matter. The animal organism can neither create nor destroy the elementary substances which enter into its structure and with which its life processes are vitally associated. It may alter the form of the combination in which the elements unite but it can bring about no change in the elements themselves.

In all living cells there are doubtless anabolic and katabolic processes going on incessantly, the two types of activity occurring within the same individual cell. Sometimes the anabolic processes will be in the ascendancy and there will be a corresponding accumulation of reserve material, whereas at other times the katabolic activities and their accompanying destructive tendencies will predominate. The conditions at any particular moment determine which of these forms of activity will receive the greatest prominence.

Metabolism is a part of that broader process or series of processes spoken of as *nutrition*, having to do more concisely with the changes taking place in the body other than those ordinarily classed under the head of secretion, excretion, etc. The metabolic processes are especially concerned with the life, growth, and functional activity of those organs and tissues which are preëminently associated with the maintenance of physiological rhythm. The muscle and nerve tissues are eminently the metabolic tissues of the body. The liver is preëminently a glandular organ endowed with metabolic power. The secretion of bile is in a measure a metabolic process, but we classify this phenomenon preferably under the head of secretion. The glycogenic function of the liver, on the other hand, is more appropriately classed as a metabolic phenomenon pure and simple; while the transformations of many crystalline amino-acids which take place in the hepatic cell with formation of urea are likewise typical metabolic processes. These facts are to be emphasized as illustrating the principle that while many processes in the body are strictly metabolic, not all are classed under this head, because of the greater convenience of treating certain of them in connection with other phenomena more easily recognizable.

It is obvious that the character of the metabolic transformations taking place in the body cannot remain exclusively of one type, if the organism or individual is to preserve its integrity and peculiar make-up. Under ordinary conditions, building-up (synthetic) processes go on side by side with the disruptive changes which liberate energy. There are, however, types of organisms that are eminently synthetic in respect to the chemical changes which are inaugurated within them; this is the characteristic of plants as a class. Anabolism and katabolism manifest themselves in both plants and animals; and it is merely in the preponder-

ance of one or the other that any essential difference in the fundamental behavior of these living forms becomes evident.

A study of the products which arise in the animal body, incidental to the metabolic activities resulting in a liberation of energy, indicates that the chemical changes involved are in large part those of oxidation and cleavage. Complex molecules of fat, carbohydrate and protein are transformed into relatively simple compounds which are uniformly richer in oxygen than the constituent components of animal protoplasm. The sulphur and phosphorus of the proteins, for example, become oxidized in their transformations within the body and reappear in the excretions as salts of sulphuric and phosphoric acids. The reactions involved are generally more complex than the illustration here selected would indicate. Many substances, however, are merely split up into simpler compounds; some are subjected to hydrolytic changes without further chemical transformation; while not a few undergo a cleavage preliminary to subsequent oxidation or synthesis, or both. In thus indicating how food or tissue constituents may be burned up in the body, the analogy with the familiar combustion processes of every-day life must not be carried too far, since combustion within the animal organism is of a peculiar and characteristic type. The reactions do not proceed with the unchecked vigor manifested in the oxidation of fuel in a fire-box. In the body we are dealing with a gradual process, regulated by conditions with which we are still largely unacquainted—a succession of chemical changes rather than a sudden and continuous burning of organic materials. Whenever they occur, the oxidations are, moreover, indirect; that is, the tissue combustion nowhere proceeds through direct intermediation of the oxygen inspired and held in the circulating fluids.

It was the recognition of these facts and the demonstration that oxidative changes for the most part do not go on in the circulating medium, which led to the abandonment of the view that the blood is the seat of these most important metabolic changes. To-day we recognize the living cell as the place where the events occur with which the story of metabolism is concerned. The details of these events are still largely unknown and the minute mechanism of the tissue changes has only partly been disclosed. The role of enzymes in the chemical organization of the cell is, however, assuming an increased importance. In agreement with the views of Hofmeister the cell may be considered as a machine working with chemical and physicochemical means. By way of illustration we may recall the manifold capacities of the liver cells. In them a series of important physiological reactions are perfected. Glycogen is built up and deposited, or released, converted, and discharged; bile pigments are elaborated from blood constituents; urea is synthesized; uric acid formed from precursors, or further oxidized; cholic acid constructed and united with glyccoll and taurin; phenols conjugated with sulphuric acid; toxic compounds chemically transformed, not to mention many less perfectly understood reactions.

It can no longer be doubted that ferments, or enzymes, are prominent in the chemical work of such cells; and, indeed, the liver tissue has been conspicuous in affording evidence of the presence of a large variety of

soluble ferments acting under a diversity of conditions. Thus, a proteolytic enzyme is conspicuous in autolysis of the hepatic tissue; lipase, maltase, laccase, amidase, oxidase, as well as ferments which facilitate reactions with the purin compounds, are further specific examples of enzymes already recognized in this tissue. Whether, indeed, the essential chemical reactions of all tissue cells are facilitated by enzymes in the way which the investigation of the liver cells has made plausible, remains to be ascertained; but it is very probable that enzymes of many kinds do exist in the different tissues and organs of the body, and, if so, they must be important factors in metabolic changes. Further, the investigations on the reversibility of enzyme action have placed fat and carbohydrate synthesis in a new light, and make the somewhat obscure anabolic processes and the redistribution of tissue constituents more susceptible of interpretation.

Income and Outgo or Exchange of Materials in Metabolism.—The study of metabolism has for its primary object the investigation of the "exchange of materials" (*Stoffwechsel*)—the extent and character of the incessant transformations which accompany and determine the changes within the living tissues. It aims to ascertain the conditions under which "the conversion of chemical tension into living energy" proceeds. Various methods have been employed to furnish the data from which the physiology of metabolism can be understood. In the first place, the activities of the individual organs and tissues have been subjected to analysis in various ways. This may yield fruitful results. For example, the blood supply to an organ may be regulated, the composition of the blood entering and leaving it may be accurately determined, and from the differences in chemical composition presented, conclusions may be drawn in regard to the storing up, utilization, or destruction of the tissue components. Such methods have been applied with success to the investigation of the gaseous metabolism of different secretory structures such as the kidneys, pancreas, and salivary glands. Quantitative measurements of the oxygen income and carbon dioxide outgo of the kidney during rest and diuresis, show that there is an increased consumption of oxygen during the increased secretory activity without any simultaneous corresponding removal of carbon dioxide (Barcroft and Brodie). During active secretion of pancreatic juice the consumption of oxygen by the pancreas is likewise increased (Barcroft and Starling). These examples indicate how perfusion of normal or "surviving" organs may facilitate the study of their metabolism. Changes of composition within the organs may be ascertained by chemical analysis, and comparisons instituted between different tissues.

Altered functions of the body and changes in the chemical behavior of certain tissues after removal of specific organs are noted in "extirpation" experiments. We need only refer to the alterations which follow the partial or complete exclusion of the liver from the circulation. Again, much has been learned, particularly in regard to synthetic and secretory processes, by comparisons of the products of specific cells with the constituents of the blood and lymph surrounding them. In this way

the metabolism of the mammary gland has been subjected to investigation, and the phenomena of milk production carefully studied. The comparison of the extent of chemical change during rest and activity in muscular and nervous tissues respectively has made it evident that the functions of these two types of physiologically active tissues are, quantitatively at least, not attended by similar metabolic changes. Corresponding studies in other cases, the salivary glands for example, have demonstrated that anabolism and katabolism may proceed simultaneously during activity, and the destruction of the cell substance during secretion be largely compensated for by a synthesis of new protoplasm (Y. Henderson).

A second method has long been employed with equal or greater success, namely, the study of the exchange of materials in the body as a whole. Indeed, it is this *total* exchange of the body which is more commonly referred to by the expression "metabolism." For many years it has been customary to investigate the metabolism of the organism as a unit, and to determine the influences of many factors upon it by ascertaining what materials have been utilized in the manifestation of the body-functions. The method is based essentially upon a recognition of the fact that certain chemical fragments of the body or its intake uniformly escape decomposition or oxidation within the organism, thereby constituting the true end-products of the chemical transformations normally occurring. A measure of the decomposition taking place is thus afforded by comparing the elements or substances which enter the body with those which leave it through various channels.

Income.—The substances which compose the ingesta of man are found to be made up in large measure of the same groups of compounds which constitute the organs and tissues of the animal body. Broadly classified, they consist of inorganic and organic materials; the former are present in relatively small amounts, while the organic compounds are found to belong in great part to three distinct groups, viz., carbohydrates, fats, and proteins. All examples of these groups contain the elements carbon, hydrogen, and oxygen; the proteins contain, in addition, nitrogen and sulphur; and phosphorus is further present, for example, in the nucleo-proteins characteristic of all cellular food materials. Many other organic compounds enter into the composition of the intake. Some, like citric and other acids, glucosides, etc., are derived from vegetable sources; others accompany or are associated with the typical foodstuffs, and are exemplified in compounds like creatin, purin derivatives, amino-acids, and numerous others. The proportion of such substances in the ordinary diet is very small in comparison with the three prominent groups or "proximate principles" mentioned. The former contain little potential energy and appear to be more important in relation to regulating or stimulating metabolic processes than in maintaining the material integrity of the body. This is equally true of the inorganic constituents of the body's intake, represented by compounds of the elements sulphur, phosphorus, chlorine, potassium, sodium, magnesium, calcium, and iron, with traces of silicon, fluorine, and iodine. Perhaps water should be classed with these substances. They are for the most part highly

oxidized compounds, and play only a subordinate part in the dynamic functions of the organism. However, they are none the less indispensable. The importance of calcium for the proper growth of bone, or of chlorides for the secretion of gastric juice, is obvious; yet too little consideration has been devoted to the possible significance of many of these elements in metabolism and the maintenance of the body's integrity.

If oxygen be added to these enumerated elements, the list of elements forming the intake will be essentially complete. A very small proportion leaves the body practically unchanged and without having entered into the metabolic processes at all. This is true not only of indigestible or undigested food residues which escape absorption and are rejected with the feces, but also of compounds which are exempt from hydrolysis, cleavage or oxidation even in health, and find their way into the excretions slightly or totally unchanged. Many alkaloids behave in this way; compounds like caffeine or creatinin are eliminated in unaltered or only slightly altered form; and many foreign pigments reappear in their original make-up in the excreta.

Outgo.—The losses of the body are continually being manifested, and include all of the elements mentioned. They occur in the form of solid, liquid, and gaseous compounds, by far the greatest part of which represents typical end-products. A smaller portion of the outgo may include products of hydrolytic cleavage; and in addition to the relatively insignificant unaltered excreta mentioned above, a portion of the substances eliminated, such as hippuric acid, represents synthetic operations carried on within the body. Aside from the familiar paths of elimination—the lungs, skin, intestines, and kidneys—the body may experience slight losses in the removal of hair or other dead epidermal structures, the discharge of ova, the ejection of semen, in menstrual flow, or in the secretion of milk. Under ordinary circumstances the latter losses are insignificant and negligible in any general account of the exchange of materials in the body. The gaseous products, leaving the body almost entirely by the lungs, are carbon dioxide and water. The kidneys eliminate the greater portion of the inorganic compounds and the nitrogenous excretory products, such as urea, creatinin, uric acid, and other purin derivatives, hippuric acid, and ammonia (in combination), as well as large quantities of water; the latter, together with traces of the preceding compounds, escapes in perspiration from the skin; while the feces contain bacteria, secretions from the wall of the gut and the glands discharging into it, and in addition indigestible and undigested food masses which have never actually entered the organism itself.

Experimental investigations have emphasized the importance of the intestine as a true excretory channel which may become even more important than the kidneys in the case of certain elements. Calcium and iron tend to leave the body in good measure through the stools in the form of phosphates, etc., as well as in the urine. To what extent the intestine may act as a compensatory organ of excretion in renal insufficiency remains to be learned. The relative importance of the various excretory channels may vary according to external circumstances. Hammarsten has grouped the losses in an adult man in the following

way: by *respiration*, about 32 per cent.; by *evaporation from the skin*, 17 per cent.; with the *urine*, 46 to 47 per cent.; and with the *feces*, 5 to 9 per cent.

METABOLIC EQUILIBRIA AND BALANCES

Under this head may be discussed the *body weight equilibrium* as well as the equilibrium relations existing between the *ingesta* and the *egesta* or the so-called *income* and *outgo*. By this latter statement we do not mean *protein equilibrium*, *carbohydrate equilibrium* or *fat equilibrium*, although these substances constitute the major portion of the solid matter of the ordinary diet. The equilibria to which we refer have to do rather with the chemical elements which enter into the structure of these various foodstuffs. Thus we speak of *nitrogen equilibrium*, *carbon equilibrium*, *sulphur equilibrium*, and *phosphorus equilibrium*. In each instance we mean the relation between the quantity of nitrogen, carbon, sulphur, or phosphorus which is introduced into the body by way of the mouth and the quantity eliminated from the body by the excretory channels and in particular by way of the kidneys, intestines, lungs, and sometimes the skin. In other words, the ingested material is balanced against the excreted material. After making careful analysis of all solids and liquids ingested and excreted we may use the data thus obtained in the preparation of a so-called balance of income and outgo. This may be rightly termed a "metabolic balance sheet." If this is to express the greatest possible number of metabolic relationships it must include data regarding the income and outgo of water and every chemical element of the dietary. We may state that, so far as we are aware, no such complete metabolic balance sheet has ever been prepared. In ordinary metabolism experiments the balances most frequently struck are those of *nitrogen*, *sulphur*, *phosphorus* and *chlorine*. In case the respiration calorimeter is available, balances for *carbon*, *oxygen*, and *water* may be added. Balances for *calcium*, *magnesium*, and *iron* are also made occasionally. When a condition of perfect balance is reached the body is said to be in *nutritive equilibrium*. As an illustration with respect to both carbon and nitrogen in a man of 70 kilograms body-weight, the following table is offered:

BALANCE OF NUTRITION ON AN ADEQUATE DIET

Income.			Expenditure.		
Foods—grams.	Nitrogen grams.	Carbon grams.	Excretions.	Nitrogen grams.	Carbon grams.
Protein . . . 100	15.5	53	Urine	14.4	6.16
Fat 100	79	Feces	1.1	10.84
Carbohydrate . 250	93	Respiration (CO ₂)	208.00
	15.5	225		15.5	225.00

Perfect equilibrium in respect to carbon and nitrogen is by no means always attained under normal conditions. The table given below is selected to give some quantitative idea of the changes incidental to metabolic processes and the balance of matter in the case of elements more commonly studied. The data are summarized from experiments by Atwater and Benedict on a man of 76 kilograms body-weight.

ESTIMATED INCOME AND OUTGO OF MATTER IN A MAN AT REST AND ON ORDINARY DIET—TOTAL AMOUNT FOR FOUR DAYS

Materials.	Weight.	Nitrogen.	Carbon.	Hydrogen.	Oxygen (esti- mated).	Ash.
<i>Income.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>	<i>Grams.</i>
Water in food . . .	3,687.6	412.6	3,275.0	
Solids in food . . .	1,892.4	64.2	944.4	139.3	695.5	49.0
Water of drink . . .	4,000.0	447.6	3,552.4	
Total	9,580.0	64.2	944.4	999.5	7,522.9	49.0
<i>Outgo.</i>						
Water in feces . . .	310.7	34.8	275.9	
Solids in feces . . .	84.6	4.9	39.9	5.7	19.1	15.0
Water in urine . . .	5,455.5	610.5	4,845.0	
Solids in urine . . .	227.9	63.4	47.2	11.9	80.5	24.9
Water of respiration, etc.	3,524.0	394.3	3,129.7	
CO ₂ of respiration, etc.	3,248.3	886.0	2,362.3	
Total	12,851.0	68.3	973.1	1,057.2	10,712.5	39.9
Outgo greater (+) or less (-) than income . .	+3271.0	+4.1	+28.7	+57.7	+3189.6	-9.1
<i>Body Material.</i>						
Protein lost, estimated to furnish	- 25.6	-4.1	-13.6	- 1.8	- 5.9	-0.2
Fat lost, estimated to furnish	- 19.8	-15.1	- 2.3	- 2.4	
Water lost, estimated to furnish	- 479.0	-53.6	- 425.4	
Ash constituents gained, furnished	+ 9.3	+9.3
Oxygen from air . . .	2,755.9	2,755.9	

Nitrogen Equilibrium and Balance.—Of all the equilibria and balances those for nitrogen are of the greatest metabolic importance. This element must enter the body in the form of protein material in order that it may be utilized in the construction of body fluids and tissues. By determining the nitrogen content of the urine we secure a rough idea of the destruction of protein material in the body. Liebig was the first (1842) to suggest the possibility of such a relationship. It remained for Bidder and Schmidt some ten years later to make the

first systematic researches along this line. These investigators used cats and dogs and demonstrated that the major part of the nitrogen content of the food was eliminated in the urine and feces. They made the following statement which is strikingly near the truth as we conceive it to-day. "Almost all the nitrogen of protein and collagen is split from its combination and carries with it enough carbon, hydrogen, and oxygen to form urea; the remaining part, containing five-sixths of the total heat value of the protein, undergoes oxidation to carbon dioxide and water which are eliminated in the respiration, the calorific (calorific) having been fulfilled." This was finally placed upon an experimental basis through the classic experiments of Voit, who was the first worker to bring an experimental animal into a condition of nitrogen equilibrium. He was likewise the first person to use the phrase "nitrogenous equilibrium." During a period of fifty-eight days Voit fed a dog 29 kg. of meat which contained 986 grams of nitrogen. Examination of the urine and feces indicated that 99.7 per cent. of this ingested nitrogen was recovered. At first thought this appears to be a very exact metabolic balance. However, nitrogen was being lost to the animal in the form of hair and scurf. According to Voit's data the nitrogen lost in these forms was equivalent to only about 1 per cent. of the total quantity of nitrogen ingested. He therefore considered it non-essential in metabolism experiments upon animals to take account of the nitrogen lost in this manner. The reviser's personal belief is that in striking a nitrogen balance all nitrogen losses which can be measured accurately should be taken into consideration. In our studies on laboratory animals it is therefore customary in the preparation of the nitrogen balance to take into account the nitrogen lost in the hair and scurf. The metal parts of the cages in which the animals are housed are also carefully washed at short intervals and the nitrogen value of this wash water determined. In this way the nitrogen present in the form of dry urinary residues and fecal dust is determined and the data included in the nitrogen balance under the head of "cage washings." As examples of typical nitrogen balances we submit the following which were obtained in investigations in the reviser's laboratory.

Nitrogen Balance, No. I (Man).

Period.	Length of period.	Nitrogen.				
		Income.	Outgo.		Gain or loss.	Average gain or loss per day.
			Food.	Urine.	Feces.	
	days.	grams.	grams.	grams.	grams.	grams.
Preliminary	2	29.308	26.267	2.716	+0.325	+0.163
Water	5	73.270	66.747	4.867	+1.656	+0.331
Final	8	117.232	99.642	8.344	+9.246	+1.156

Nitrogen Balance, No. II (Dog).

Period.	Length of period.	Nitrogen.						
		Income.	Outgo				Gain or loss.	Average gain or loss per day.
			Food.	Urine.	Feces.	Hair.	Wash.	
	days.	grams.	grams.	grams.	grams.	grams.	grams.	grams.
Preliminary	4	16.40	14.95	1.01	0.32	0.24	-0.12	-0.03
Anesthesia	2	8.20	8.75	0.64	0.14	0.14	-1.47	-0.74
Final	4	16.40	15.34	1.31	0.28	0.32	-0.85	-0.21
Total	10	41.00	39.04	2.96	0.74	0.70	-2.44	-0.24

An examination of the second balance shows that about 2 per cent of the ingested nitrogen of the preliminary period was lost in the form of hair and scurf, whereas the cage washings accounted for an additional $1\frac{1}{2}$ per cent. A somewhat similar relation holds for the other periods. The data from the metabolism studies made by the reviser upon laboratory animals during a period of ten years indicate that in such tests a quantity of nitrogen equivalent to from 2 per cent. to 4 per cent. of the total quantity ingested was recovered in the form of hair, scurf, and cage washings. Certainly if we wish to reduce the error in our nitrogen balance to the lowest possible limit we must take cognizance of the nitrogen in the forms indicated. Another source of error in nearly all nitrogen balances is the absence of all data as to nitrogen lost in cutaneous excretions. In animals confined in small cages allowing of but slight movement the loss of nitrogen through the skin is probably negligible. In the case of a man taking vigorous exercise, the case is decidedly different. It has been shown by Benedict that a man doing moderate work will eliminate 0.13 gram of nitrogen *per hour* through the skin, whereas in case the muscular exertion is severe the hourly cutaneous nitrogenous excretion is increased to 0.22 gram. The similar value for a resting man is but 0.003 gram. The securing of at least an approximate nitrogen equilibrium is an essential preliminary to nearly all forms of accurate and dependable metabolism studies.

When an investigator is to use a man or a lower animal as the subject in a nutrition test it is essential that a definite fundamental standard should be attained as a basis for the experimental study which is to follow. This standard condition is nitrogen equilibrium. It is a normal condition for an adult. If left free to choose their diet the majority of adult men will so regulate their choice as to maintain an approximate nitrogen equilibrium. One man may ingest much more nitrogen than another of approximately the same size and yet each may be at nitrogen equilibrium. The fact that we are able to secure nitrogen equilibrium at different nutritional planes is an important one in metabolism. We may for example bring a man to equilibrium on a diet containing 12 grams of nitrogen per day and subsequently increase this diet to one containing 24 grams of nitrogen per day and again secure nitrogen

equilibrium at this higher nutritional plane. The normal adult animal organism will not store nitrogen to any appreciable extent or for any considerable length of time no matter how much nitrogen may be introduced. On the other hand the growing individual as well as the individual who is convalescing will store considerable nitrogen.

Many fallacious deductions may be made in the interpretation of nitrogen data secured from subjects who were not in nitrogen equilibrium at the outset of the metabolism study. We say, for example, when a man ingests more nitrogen than he excretes, that a certain quota of nitrogen is being retained in the body or "stored" as it is generally called. On the other hand, if he excretes more than he ingests body tissue is being disintegrated to furnish the extra nitrogen. Now, let us say that we start our experiment with the subject ingesting two grams of nitrogen per day more than he excretes. We study the influence of some certain factor, let us say a drug for example, the ingestion of this drug continuing over a period of days or weeks. At the end of the period we find our subject is at nitrogen equilibrium. How are we to interpret the influence of the drug? As we have said, a condition of nitrogen equilibrium is a normal one for the adult organism. Here we have an adult organism brought into equilibrium while ingesting the drug. On the other hand the nitrogen balance shows us that the subject is now losing two grams of nitrogen per day more than he was losing during the preliminary period. Has the drug had a deleterious influence upon the nitrogenous tissues of the organism thus causing them to disintegrate more rapidly than usual? It might at the same time be argued that this subject would have come to nitrogen equilibrium upon this diet anyway even had the drug not been included in his dietary. This might well have been, inasmuch as we have seen that it is ultimately possible to bring individuals to equilibrium upon diets which at the outset may produce very pronounced plus or minus balances. We may give at least three interpretations to the data from the drug test just outlined. In the first place we may consider its effect as detrimental, inasmuch as it has caused a more rapid disintegration of body tissues; in the second place, we may consider it as beneficial to the organism, inasmuch as it has brought about a condition of nitrogen equilibrium which is accepted as the normal state for adult individuals, and in the third place we may consider that the drug has had no influence whatever, inasmuch as we would ultimately have secured nitrogen equilibrium even without the addition of the drug to the diet. All this uncertainty of interpretation might have been eliminated had we brought our subject to a condition of nitrogen equilibrium before feeding the drug. In this event the sensitive metabolic equilibrium would have been influenced either favorably or unfavorably and the nitrogen balance would be our talisman.

In what manner may we bring an individual to nitrogen equilibrium in the shortest time? It is customary to give a simple diet, let us say crackers, milk, and butter, these ingredients being fed in uniform amount from day to day. The diet is analyzed and the quantities of the constituents fed will be regulated so as to feed the individual approximately the same amount of nitrogen per day as he has been accustomed to

ingest. The urine and feces are collected and analyzed and a nitrogen balance struck. If the balance shows the body to be losing nitrogen it is taken as an indication that the diet is not sufficient. The diet is then increased to cover this loss, and the urine and feces again examined. In this way a very exact equilibrium may be secured. In case the nitrogen balance should show the individual to be excreting less nitrogen than he was ingesting it would indicate that the diet was too heavy and that a storage of nitrogen was taking place. The diet would then be reduced somewhat and a new test made.

Although we seldom use the phrase *protein equilibrium* yet it is nevertheless protein material we have in mind primarily when we discuss nitrogen equilibrium. The nitrogen excretion serves as an index of the course of protein metabolism in the body. By the application of a simple factor we may translate our nitrogen data into terms of protein. This factor is 6.25. We consider that protein contains on the average 16 per cent. of nitrogen. Therefore if we multiply the weight of nitrogen in grams by the factor 6.25 we obtain the weight of protein equivalent to the nitrogen value. This factor has been in use for many years and was suggested at a time when it was generally believed that practically all protein substances contained approximately 16 per cent. of nitrogen. Since this time, and particularly since the chemistry of the vegetable proteins has been more thoroughly investigated, we know that there are many proteins which contain much more than 16 per cent. of nitrogen; in certain instances this is above 20 per cent. The proper factor for a protein containing 20 per cent. of nitrogen is of course 5. Therefore we introduce a very appreciable error when we use the factor 6.25 in the translation into protein values of the nitrogen values derived from the analysis of such proteins. At the same time there are certain well-known proteins which contain *less* than 16 per cent. of nitrogen. Here too we are in error when we apply the factor 6.25. In the case of caseinogen for example, which contains 15.7 per cent. of nitrogen, the factor should be 6.37. To be strictly accurate it is evident that we should utilize a different factor for each individual protein, so long as the actual nitrogen content of such protein varies.

It is no doubt true, as pointed out by Osborne and Mendel, that "nitrogen balances may, at times, prove singularly deceptive, and give apparently favorable indications of equilibrium, although the real nutritive status of the animal may be less promising." For example it is possible, under some conditions, to obtain a positive nitrogen balance at one stage of an experiment and a negative nitrogen balance at another stage without change of diet.

Carbon Equilibrium.—The carbon balance is manipulated in much the same way as the nitrogen balance. An individual is in carbon equilibrium when the total carbon of the excreta in the forms of urea, carbon dioxide, etc., is equivalent to the ingested carbon. Nitrogen equilibrium is not necessarily accompanied by carbon equilibrium. Thus we may have a marked gain or loss of carbon by an individual whose nitrogen intake is practically balanced by the outgo. In general terms a minus carbon balance indicates a loss of fat or glycogen, whereas

a plus carbon balance indicates that the stores of fat and carbohydrates are being increased. Both fat and glycogen may be stored in comparatively large amounts by adults as well as by younger individuals. The conditions surrounding the storage of nitrogen do not hold for carbon. The latter element may be retained in comparatively large quantity under proper conditions, whereas the nitrogen storage is held at a minimum in adults under practically all conditions. Carbon balances are possible only in connection with respiration calorimeter experiments.

Phosphorus, Calcium, Magnesium, and Sulphur Balances.—Relatively little attention has been given to the balance of other elements, notably sulphur and phosphorus, in metabolism. The data are obtainable in a similar way, but the conclusions are by no means equally clear and concordant. Both of these elements are eliminated, for the most part, in the form of highly oxidized compounds, through the kidneys and intestine. Volatile compounds, like hydrogen sulphide, are formed normally in traces only. Although very small quantities of simple sulphur compounds, like sulphates, are found in food and water, almost the entire intake of this element occurs in the form of protein compounds containing from 0.3 to 2.5 per cent. of it. Within the protein molecule the sulphur presumably exists in the complex represented by cystin. In the excretions it is found as inorganic or ethereal sulphates and in minor degree in the form of less highly oxidized compounds whose composition is at present unknown. Under normal conditions, metabolism and elimination of sulphur tend to run parallel with that of nitrogen, although the variable content of sulphur in proteins renders a strict comparison impossible. Otherwise expressed, the ratio between nitrogen and sulphur is liable to vary with the kind of protein substance disintegrated, the proportions in the latter varying all the way from 44 to 1 in oxyhemoglobin to 5 to 1 in tendomucoid.

The rôle of phosphorus is even less certain than that of sulphur. Under ordinary conditions, the phosphorus intake is confined very largely to the phosphates of the food. Phosphorus occurs, however, in the phosphorized proteins, like the casein of milk and vitellin of the egg-yolk, as well as in the nucleoproteins, the complex substance lecithin, and organic phosphorus compound of vegetable origin. The body fluids and tissues abound in inorganic phosphates, which are especially conspicuous in the bones. The distribution of phosphorus in the important tissues of man has been estimated by Voit as follows: In nervous tissues, 12 grams; in the muscles, 130 grams; in the bones, 1400 grams. These figures indicate the degree to which the various parts may be expected to participate in the metabolism of phosphorus when either loss or retention of the element occurs. At one time it was assumed that the elimination of phosphorus might be taken as an index of changes in the nervous system. At present, however, physiologists are more inclined to associate disturbances in the phosphorus balance with changes in other tissues. In view of the presumably slight metabolic activity in the bones of adults during health, the elimination of phosphorus not directly attributable to phosphates ingested has lately more frequently been attributed to katabolism of the nucleoprotein constituents of

the tissues. Since the active cells of the body everywhere contain the phosphorus-holding nucleoproteins, the possible significance of phosphorus elimination in its relation to cell katabolism cannot be overlooked. From the synthetic side the question of the importance of phosphorus for the anabolism of cell protoplasm at once suggests itself. Phosphorus is excreted almost entirely in the form of phosphates of the alkalis and alkali earths, minimal quantities escaping in the form, perhaps, of glyceryl-phosphate.

Organic phosphorus compounds are of at least five kinds, *phosphoproteins*, *nucleic acid*, *lecithins*, *phytin* (phosphoric acid in combination with inositol as the calcium-magnesium salt), and *hexosephosphate* (phosphoric acid combined with a hexose). Of these the phosphoproteins are confined to the animal kingdom where they form the main protein food supply of suckling mammals and embryo birds. Nucleic acid is present in the nuclei of both plant and animal cells. Lecithins occur principally in animals. Phytin or phytic acid has been found only in plants, while hexosephosphate is formed in yeast alcoholic fermentation. Little is known regarding the metabolism of these substances. It is believed that plants possess the power of synthesizing organic phosphorus compounds from inorganic phosphates, and *vice versa*. However, little is known as to the exact mechanism of these changes or of the enzymes involved. Recent experiments indicate that the *animal* organism may also synthesize organic phosphorus from inorganic sources. However, whether the phosphorus be ingested in the form of organic or of inorganic compounds the urinary phosphorus is almost entirely inorganic (Mathison; Plimmer, Dick, and Lieb; Gregersen; Sherman), whereas the fecal phosphorus is mainly in this form.

That the phosphorus of phytin (phytic acid) is excreted as inorganic phosphate has been shown by Mendel and Underhill, Scofone, Giacosa, and Horner. Fingerling fed ducks for alternate periods on diets which furnished the phosphorus in the form of organic and inorganic compounds respectively. There was no apparent difference in the number of eggs laid nor in the lecithin and nuclein content of these eggs. Organic phosphorus had evidently been synthesized from inorganic sources. This same investigator likewise demonstrated that the milk of goats fed on a diet containing organic phosphorus was of the same phosphorus content as milk from the same animals fed inorganic phosphorus. McCollum, Halpin, and Drescher have demonstrated the synthesis of lecithins in hens fed on a diet free from lecithin.

The findings of Plimmer indicate that the most active tissue in the hydrolysis of organic phosphorus compounds is the intestinal mucosa. The pancreatic extract hydrolyzed only phosphoprotein and this only two-thirds of the way to completion; the final stage of hydrolysis being brought about in the human intestine by erepsin of the intestinal juice. Attention may be called to the fact that phosphoprotein being different in constitution from the other phosphorus compounds examined, which are esters of phosphoric acid, probably accounts for its unique action toward the pancreatic extract. Plimmer believes that "The organic phosphorus compounds are . . . assimilated as inorganic phosphate

and the organic radical with which the phosphorus is combined." It is apparent that the nutritive value of organic phosphorus compounds depends entirely upon the *character of the organic radical* to which the phosphoric acid is joined.

The differences in the behavior of the different types of phosphorus compounds in metabolism is well illustrated by the following balance-sheet for phosphorus and nitrogen, taken from experiments on a dog fed with the same quantities of these elements contained in the form of the phosphorized protein casein, and the phosphorus-free protein edestin and phosphates, respectively (from Zadik):

Period.	Nitrogen.	Phosphorus.	
I	+12.2	+0.45	Feeding with casein.
IV	+ 6.1	+0.34	
II	- 2.4	-0.71	Feeding with edestin and phosphates.
III	+ 5.9	-0.65	

The balance of phosphorus in metabolism demands special interpretation. It appears, furthermore, as if there is far less tendency toward equalization between intake and output than has been found so conspicuous in the case of nitrogen and sulphur. The organism is capable of storing up (synthetically or otherwise) comparatively large quantities of phosphorus during longer periods of time, without close relation to simultaneous changes in the metabolism of nitrogen. All the foregoing facts must be taken into consideration before any wide-reaching attempt is made to connect the excretion of phosphates with the katabolism of any specific phosphorus-containing constituents of the body like the nucleoproteins, osseous or nervous tissues.

In general, the metabolism and balance of sulphur will be found to run approximately parallel with that of nitrogen. With phosphorus the parallelism is less apparent, and in no case is the gain or loss here great enough to justify calculations of the materials stored or broken down. Finally, the relatively large proportion of phosphorus leaving the body in the feces is an illustration of the importance of the intestine as an excretory channel for some compounds.

BALANCES FOR CALCIUM, MAGNESIUM, PHOSPHORUS, SULPHUR,
AND NITROGEN (GRAMS)

		Mrs. McD.				
		Seven days.				
		CaO.	Mgo.	P ₂ O ₅ .	S.	N.
Ingestion	Total	14.925	2.768	27.804	4.283	63.770
	Per day	2.132	0.395	3.972	0.612	9.110
	In urine	0.126	0.229	9.963	5.644	64.070
Excretion	In feces	7.388	0.913	8.572	0.512	0.380
	Total	7.514	1.142	18.535	6.156	64.450
	Per day	1.073	0.163	2.648	0.879	9.210
Retention	Total	7.412	1.626	9.269		
	Per day	1.059	0.232	1.324		
	Percentage	49.700	58.700	33.300		
Loss	Total	1.873	0.680
	Per day	0.268	0.097
	Percentage	43.800	1.060

Balances of calcium, magnesium and phosphorus are of particular significance in bone diseases. The balance for calcium, magnesium, phosphorus, sulphur, and nitrogen obtained in a case of osteitis deformans is shown on page 563 (Da Costa, Funk, Bergeim, and Hawk).

ENERGY METABOLISM

The simple comparison of the income and outgo of matter, or the investigation of the synthesis or combustion of protein, fat, and carbohydrate in the body, leaves many of the problems of nutrition completely unsolved. They merely afford incomplete data from which to estimate the actual needs of the body for its work or to determine the relative nutritive value of the different types of ingesta under varying conditions. When, however, it is remembered that the *chemical transformations of the body are accompanied by physical phenomena* and that the exchange of materials goes hand in hand with a *transformation of energy*, the study of metabolism presents a new and broader aspect. We are thus prepared to take a new view of the organism as a mechanism in which, incidental to the life-processes, potential energy becomes kinetic. The chemical energy latent in the food and body materials is liberated by oxidation or cleavage in the form of work and heat. It must now be apparent that food has two functions in the body, namely, the building, or repair, of tissues and the yielding of energy. The uses of the food and its service to the organism are thus extended beyond the conception which the consideration of transformation of materials alone has suggested. *Metabolism implies a transformation of energy as well as an exchange of materials.*

It is in connection with the chemical changes that the transformation of energy from a potential to a kinetic form takes place; and precisely as the nature of the chemical changes is imperfectly understood, so the physical changes require more extensive investigation in anticipation of a complete interpretation of how they occur. The oxidative, or combustion processes are unquestionably the most important, although undoubtedly potential energy also becomes kinetic in the cleavage of complex compounds to simpler ones. But the physiological energy transformations correspond with the chemical processes of metabolism in being apparently more complex than is the case in combustion outside of the body, and also more gradual. In general the end-products of combustion within the organism are the same as those obtained by burning the compounds in oxygen; and there is every reason to believe that the quantity of potential energy transformed in the combustion of any substance within the body will be the same as that noted by the usual physical measurement in the laboratory. The manifestations of life are accompanied by the *transformation of energy*. This energy is obtained with the food, in the form of chemical compounds; it is in the manifold transformations of the latter that heat production, body work, and electrical phenomena have their origin. The energy so liberated manifests itself continually in such ways as the beating of the heart, the respiratory movements, peristaltic movements, etc., ultimately being

lost to the body in external work, heat, or water vapor. A small part escapes in the organic constituents of the urine and feces.

It is quite plain that just as the cells require certain *materials* to replace the waste and disintegration going on within them, they also need the *energy* which they derive from the contributions brought to them by the circulating fluids of the body or stored up within themselves. The demands for energy may, however, be satisfied in more diverse ways than is the case with the demand for materials. For while there are certain compounds, like the proteins, which are essential for the maintenance of cellular life, the body can satisfy its energy-yielding requirements from a variety of sources with equal readiness. The metabolism of matter accordingly is characterized by certain *qualitative* features; that is, under determined conditions definite kinds of compounds must be available if the functions are not to suffer deterioration. In the metabolism of energy, on the other hand, *quantitative* relations play the important part. The potential energy must be renewed and adequate provision made for the maintenance of body temperature and activity. Proper quantities of nutrients must be furnished, without emphasizing the type of compound in which the energy is stored. The fact that in man and many other organisms energy is liberated by cleavage with intermediation of respired oxygen has, as Rubner pointed out, a distinct advantage; for *oxidative* cleavages render latent energy available in greater proportion than many other forms of decomposition. Thus, the heat afforded in such living processes as alcoholic fermentation or lactic acid fermentation is comparatively slight. And if the ferment organisms involved in them regulate their food supply in correspondence with the proportion of energy set free in the decompositions which they incite, it becomes apparent why they afford so large a yield of fermentation products.

Since the organic foodstuffs contain a store of potential energy which may become transformed sooner or later in metabolism, we may take this energy as a measure of their "fuel value," that is, their value in accomplishing work and forming heat when they are metabolized in the body. The quantity of heat set free when a given organic food compound is burned with oxygen in a calorimeter is an equivalent and measure of its potential energy. We may, therefore, appropriately estimate the fuel value of a nutrient substance by its heat of combustion. And inasmuch as the greater portion of the energy changes in the body result in the liberation of heat, it has become customary to measure these transformations by similar heat units. The "heat of combustion" of a substance is expressed in large calories or kilogram-degree units of heat, and in small calories, *i. e.*, gram-degree units of heat. The former represent the quantity of heat required to raise 1 kilogram of water 1° C.; the small calorie represents the heat required similarly to raise the temperature of 1 gram of water. Therefore, 1000 small calories = 1 large calorie.

In the calorimeter, substances are burned up in an atmosphere of oxygen; as is the case in the body, fats and carbohydrates are decomposed to carbon dioxide and water. Proteins yield nitrogen, sulphuric

(and sometimes phosphoric) acid, in addition to carbon dioxide and water. In metabolism the combustion of proteins is less complete. The nitrogenous moiety of the molecule is eliminated in the form of less simple bodies. We have, accordingly, to distinguish between their physical fuel value and that determined by direct measurement in the calorimeter. This physiological fuel value of the proteins can be ascertained by subtracting from the fuel values of the total material, the heat of combustion of the incompletely oxidized excretory products—such as the urea, uric acid, creatinin, etc., of the urine—and the unutilized nitrogenous residues of the food excreted by the intestine, corresponding to the protein considered. The loss of energy represented by the normal incomplete combustion of the proteins may amount to 22 to 28 per cent. (Rubner).¹ It may be added that when a portion of the intake is anabolized or stored in the body, its potential energy is likewise held in reserve; and when katabolism of the tissues proceeds uncompensated from without, the metabolism of energy is proportionate to the yields required of the particular compound which is burned or split up, with due allowance for the corrections suggested above.

The calorimetric researches of Berthelot, Stohmann, Rubner, Atwater, and their associates have given us a large number of data relative to the potential energy or fuel value of many compounds. Relatively few figures apply to the isolated foodstuffs—the proteins, fats, and carbohydrates. A few typical examples are given below:

HEATS OF COMBUSTION OF ORGANIC SUBSTANCES (PER GRAM)

Proteins.	Calories.	Fats.	Calories.
Beef	5.65	Beef fat	9.50
Protein of meat	5.65	Mutton fat	9.51
Egg albumen	5.71	Lard	9.59
Casein of milk	5.78	Butter fat	9.27
Gluten of wheat	5.95	Olive oil	9.47
Gelatin	5.27	Fat of cereals	9.30
Vegetable protein	5.00		
Carbohydrates.	Calories.	Other organic substances.	Calories.
Pentoses	4.00	Urea	2.52
Dextrose	3.75	Alcohol	7.07
Cane sugar	3.96	Citric acid	2.39
Milk sugar	3.86	Creatin	4.27
Starch	4.20	Uric acid	2.62
Dextrin	4.11	Leucin	6.53
Glycogen	4.19	Feces (average)	6.20

Such figures, by themselves, give little idea of the actual fuel value or available energy attributable to the nutrient substances as they are ordinarily consumed. The diet of man consists of foods of complex composition, rather than definite chemical compounds; and it is only under experimental conditions that the pure foodstuffs enter into consideration. The actual amount of energy which the body can derive from a given diet depends upon a variety of factors, chief among which are the quantities and chemical energy of the foodstuffs *available* and the amount of incompletely oxidized material rejected in the excretions.

¹ Tigerstedt has noted as a general rule that the percentage loss of calories in the feces is roughly equal to the figure obtained by estimating the percentage relation of the dry solids of the feces to the total dry solids of the food ingested.

If we examine the figures showing the availability or utilization of foods we see that only a *portion* of the materials ingested is actually made available or utilized in metabolism. The *available energy* of the fats and carbohydrates is the total energy of their available material. In the case of the proteins the digested and absorbed material is not completely broken down and oxidized; the *available energy* of this group is therefore represented by the difference between the total and that of the excreta which escape unoxidized. Such general statements as these are subject to minor modifications, the discussion of which would be unprofitable in this place. Rubner proposed a series of factors by means of which the energy-yielding value of the foodstuffs could be calculated, namely:

1 gram of protein yields	4.1 calories (large)
1 gram of fat yields	9.3 calories
1 gram of carbohydrate yields	4.1 calories

Outside of the three groups included above, few other food materials have any significant interest. Alcohol, certain amino-acids, and a few compounds of the fatty acid series, such as asparagin, may enter into the diet at times; but the other organic substances need not receive serious consideration as sources of energy or matter. Some of them liberate energy as heat when they are burned with oxygen in the calorimeter. In the body they cannot serve as sources of energy, because they are either not absorbed or fail to be katabolized. To this group belong the inorganic salts and water, which furnish no energy to the organism, however indispensable they may be for its functions.

It is apparent that proteins and carbohydrates furnish practically the same yield of energy in metabolism, in contrast with the fats which afford far more heat per unit of material. If the composition of the ingesta, with reference to the content of proteins, carbohydrates, and fats is known, the fuel value of the mixed food materials can readily be calculated, and approximate corrections made for the availability of the different constituents.

With this introduction to the consideration of the transformation of energy in the living body, we may proceed to consider some of its phenomena and the laws which govern them in their application to metabolism. No adequate treatment is possible without a thorough understanding of the principle of the conservation of energy. The circulation of energy is intimately associated with the circulation of the elements in the living body as well as in the inorganic world about us. If it is as impossible to destroy energy as it is to destroy matter, we must expect, when the chemical potential energy of the food or the body tissues is used up, to find an equivalent amount of other forms of energy appearing in the body. Energy itself cannot be directly observed and pursued; but we can measure it by its manifestations of motion, whether it be a visible motion of masses of matter or that invisible motion of infinitely smaller particles which is spoken of as heat.

In accordance with this statement, it is to be noted that the body is continually *producing heat*, and furthermore it is engaged in movement and *performing work*. These are the essential manifestations of a trans-

formation of energy. It has frequently been suggested that in the performance of *psychical functions* also, chemical potential energy must be liberated. We are, however, unable to say definitely whether the phenomena of consciousness follow the law of the conservation of energy. There is no evidence in man and the higher animals that energy is liberated in the form of light or electricity. At any rate, if such transformations do occur, the energy must finally leave the body as heat, or in some form which we do not at present recognize.

Balance of Energy.—As the body receives its energy supply solely in the form of chemical compounds, it should be possible to determine experimentally the *balance of energy* in the organism, provided that the physical and chemical changes taking place occur in obedience to the laws of the conservation of energy and matter. The essential data for comparison are, obviously, the income and outgo of energy. The income can be estimated in terms of calories or heat units after corrections have been made for the loss of potential energy in the corresponding incompletely burned metabolic end-products. When the tissue constituents themselves furnish the energy liberated, the quantitative relations can be established by ascertaining the exchange of materials which has ensued; and thus the energy of the katabolized compounds can be calculated.

In the measurement of the *outgo of energy* from the body, the quantities to be ascertained are the heat given off from the body and the external muscular work, which can in turn be converted into terms of heat units. The muscular work of the internal organs is transformed into heat before it leaves the body. Briefly reviewed, the factors to be determined in preparing the balance-sheet of the income and outgo of energy are: (1) Potential energy of the organic compounds of food and drink; (2) potential energy of organic compounds of feces, urine, and products of perspiration and respiration; kinetic energy given off as heat and external muscular work (and other possible forms).

Since the study of the balance of matter gives the data from which the gain or loss of protein, fat, and carbohydrate in the body can be estimated, a calculation of the fuel value of the corresponding foodstuffs can readily be made. Furthermore, the potential energy of the ingesta can be determined directly by calorimetric methods. Thus the conditions are given for comparing the energy available in metabolized materials with the quantity of heat generated by the body. Rubner was the first to show that the quantity of heat given off by the body is almost exactly equivalent to that calculated from the available potential energy of the foodstuffs actually metabolized, under various conditions of diet. Figures from his experiments are quoted:

Character of diet	Number of days.	Heat units calculated.	Heat units found.	Percentage difference.
No food	{ 5	1296.3	1305.2	-1.42
	{ 2	1091.2	1056.6	
Fat	2	1510.1	1495.3	-0.97
Meat and fat	{ 8	2492.4	2488.0	-0.42
	{ 12	3985.4	3958.4	
Meat	{ 6	2249.8	2276.9	+0.43
	{ 7	4780.8	4769.3	

COMPARISON OF INCOME AND OUTGO OF ENERGY IN 45 METABOLISM
EXPERIMENTS COVERING 143 EXPERIMENTAL DAYS—AVERAGE
AMOUNTS PER DAY

Subject and kind of experiment.	Dura- tion.	Net income potential energy of material oxidized in the body).	Net outgo (kinetic energy given off from the body).	Difference in terms of net income.	
Ordinary Diet.					
Rest Experiments.	Days.	Calories.	Calories.	Calories.	Per cent.
7 Experiments with E. O. .	25	2268	2259	- 9	-0.4
1 Experiment with A. W. S.	3	2304	2279	-25	-1.1
3 Experiments with J. F. S.	9	2118	2136	+18	+0.8
1 Experiment with J. C. W.	4	2357	2397	+40	+1.7
Average of 12 experiments with E. O., A. W. S., J. F. S., and J. C. W.	41	2246	2246	0	0.0
Work Experiments.					
2 Experiments with E. O. .	8	3865	3829	-36	-0.9
4 Experiments with J. F. S.	12	3539	3540	+ 1	0.0
14 Experiments with J. C. W.	46	5120	5120	0	0.0
Average of 20 experiments with E. O., J. F. S., and J. C. W. .	66	4682	4676	- 3	-0.1
Average of all rest and work experiments (32) with ordin- ary diet	107	3748	3745	- 3	-0.1
Special Diet.					
Rest Experiments.					
6 Experiments with E. O. .	17	2313	2319	+ 6	+0.3
3 Experiments with A. W. S.	6	2308	2356	+48	+2.1
1 Experiment with J. F. S. .	3	2124	2123	- 1	0.0
Average of 10 experiments with E. O., A. W. S., and J. F. S.	26	2290	2305	+15	+0.7
Work Experiments.					
1 Experiment with E. O. .	4	3922	3928	+ 6	+0.2
2 Experiments with J. F. S.	6	3583	3552	-31	-0.9
Average of 3 experiments with E. O. and J. F. S.	10	3719	3702	-17	-0.5
Average of all rest and work experiments (13) with special diet	36	2687	2695	+ 8	+0.3
Average of all rest and work experiments (45) all diets .	143	3481	3481	0	0.0

The living body controls no permanent sources of energy other than those furnished by the food. More recently the demonstration of this

fundamental principle has been furnished in the case of man under various conditions of rest and activity, by Atwater and his associates. The results of 45 experiments covering one hundred and forty-three experimental days are summarized in the table on page 569 (Atwater and Benedict). The remarkable average agreement between the theoretical and actual changes of energy in the human body evidenced by these figures, indicates that the law of the conservation of energy obtains here precisely as *a priori* considerations would lead us to expect. It is evident that in the study of metabolism, the calorimetric method is capable of furnishing data quite comparable in value with the facts learned by study of the purely chemical changes.

It is instructive to examine the relative participation of different paths in the discharge of energy from the body. The significant features are plainly indicated in the summary prepared from the experiments of Atwater and Benedict. The important rôle of the body surfaces in the dissipation of heat is made apparent.

PERCENTAGE OF ENERGY GIVEN OFF FROM THE BODY IN DIFFERENT WAYS

Path of heat elimination.	Rest, fasting.	Rest, with food.	Work experiments.
By radiation and conduction . . .	73.4	74.4	71.4
In urine and feces	0.9	1.4	0.6
In water vaporized from lungs and skin	25.7	24.2	18.4
Heat equivalent of external mus- cular work done	9.6

Replacement of Nutrients.—The conception of metabolism as a process in which the body transforms the potential energy of the food in accord with well-known physical and chemical laws, suggests the possibility that different substances might replace one another, as nutrient materials, in proportion to their energy-yielding or fuel value. From this point of view, the content of energy (as expressed in the available heat of combustion) becomes the crucial factor in estimating the importance of any food; the demands of nutrition are satisfied by supplying energy to the body. Limitations to such a conception at once arise, as, for example, the impossibility of maintaining life unless at least a minimum of protein is furnished to make good the continued degradation of the nitrogenous tissues. Yet the general idea that the foodstuffs can replace one another to a very large, if not an unlimited, extent in metabolism was long ago suggested. With the exception of the slight differences in the case of the proteins, experiments show a satisfactory equivalence between the actual heat production and the computed values. From this we may conclude not only that the foodstuffs yield heat in the body in proportion to their estimated fuel value, but that the nutrients may replace each other in proportions corresponding to their heat value. By the latter is of course here understood their “available” or “physiological” heat value—“metabolizable energy,” as expressed by Armsby. The quantities which thus replace each other are said to be *isodynamic*. Accordingly, it follows that the bodies of the higher animals do not require the same quantities of different foods for

the purposes of metabolism; but they obey a law of *isodynamic replacement* according to which the foodstuffs may be substituted for one another in inverse proportion to their available energy.

These observations and deductions which place food values in a new light and emphasize the energetics of metabolism so strikingly, have received wide acceptance. Renewed investigation has, however, demonstrated that the foodstuffs are strictly isodynamic only within certain narrow limits and under definite conditions. The animal body is by no means a machine so simple that it transforms energy with such indifference toward the *kinds* of materials metabolized. Whenever transformations go on, the yield of heat is strictly proportional to the energy-content of the materials metabolized; but the regulation of the kind of food or body constituents burned up is apparently far more complex than was formerly assumed. A slight departure from theoretical conditions has already been noted incidentally in the case of the proteins. Rubner gradually modified his earlier conception of the isodynamic replacement of the foods to apply strictly only to small amounts of the latter under conditions approaching the maintenance ration, *i. e.*, conditions of nutritive equilibrium. With these reservations the general idea expressed above forms an important part of the current theories of nutrition, and is capable of at least partial demonstration.

We cannot undertake to review in detail the criticism and changes which the preceding ideas have experienced since they were first promulgated. A difference between the effects of small and large amounts of food was early discovered. Moreover, the work of digestion and assimilation varies widely with different types of food, and introduces a new source of heat. In some cases the heat thus produced is utilized to warm the body, and less energy is withdrawn from that stored in the tissues. At other times the excess of heat arising from the work of digestion cannot thus be compensated for. Furthermore, environmental conditions as well as feeding play a rôle in the adjustment. In a general way it may be pointed out that materials containing the same amount of total energy may require the expenditure of very unequal amounts of energy for their digestion and utilization; and although the general laws of energy naturally support the theory of isodynamic replacement, the discrepancies largely hinge upon the factors which determine the net *available* energy in each case. When large, but isodynamic, quantities of different foodstuffs are compared, they exert unequal energy transformations. Proteins are especially peculiar in this respect, in stimulating heat production. Without attributing it specially to the work of the digestive or other glands, Rubner has applied to this function the expression *specific dynamic action*. The isodynamic values of fats and carbohydrates show a tendency to be maintained; but when the proteins are exhibited in excess they exert a specific dynamic action in provoking a disproportionate transformation of energy with liberation of heat. A further example of an apparently similar specific action is seen when alcohol is administered. The possibility of its combustion and an isodynamic replacement of ordinary nutrients seems to depend upon conditions which involve both the individual and the quantities administered.

Lusk has suggested that the increase in metabolism following protein ingestion is due to the *mass action of amino-acids acting as stimuli upon cellular protoplasm*.

When we consider the needs of the body from the standpoint of the changes of energy going on within it, too much emphasis must not be placed upon absolute figures or fixed proportions. As elsewhere in physiology, so in the study of metabolism, adaptation processes are met with. The specific-dynamic action of proteins, in inaugurating a liberation of energy far greater than the small plus of digestive work entailed by them can account for, applies broadly only to the adult. In the young and growing organism, a different disposition of proteins is made. We are dealing, in the animal body, with a complicated apparatus the workings of which cannot be expressed in simple laws.

Mechanical Efficiency of the Body.—Before leaving the consideration of the body as an energy-transforming mechanism, we may refer to its efficiency and capacity for work. Part of the energy stored within the organism is expended in maintaining physiological functions and in the case of the heart the work done can readily be calculated. The energy involved in these processes is, however, ultimately transformed into heat, in which form it leaves the body. In speaking of the working capacity of the body we ordinarily refer to external muscular work. It is a familiar fact that in the performance of an ordinary steam-engine a relatively small fraction of the energy furnished in the form of fuel can be transformed into mechanical energy, the greater portion being dissipated as heat. The average efficiency of such engines, that is, the proportion of the expended energy which appears as work done, is under 15 per cent. The determination of this ratio in man is attended with considerable difficulty. Experiments by Atwater and Benedict, on a bicycle rider, gave 19.6 as the efficiency percentage.

Other experiments in which the necessary data have been accurately determined have given efficiency figures of a similar order. There is no evidence at present to indicate that mental "work" is attended by any liberation of energy peculiar to it, or that mental excitement *per se* induces any noticeable metabolism. The results may be expressed in a general way by saying that "for every calorie which was transformed into external muscular work, four calories or more were transformed into heat, and left the body in that form. Whether the same ratio of efficiency applies to the muscular work of the internal organs has not yet been ascertained. Calculations of the total energy metabolized and the external work done during prolonged and severe muscular work by trained athletes (bicycle riders) indicate a far larger efficiency; but the results are attended with too great a degree of uncertainty to receive serious consideration without further corroboratory experimental evidence." There is little doubt that the utilization of energy in doing work is favorably affected by training.

Heat Production.—The subject of the metabolism of energy requires a brief mention of its relation to heat production. To what extent heat is produced for its own sake, *i. e.*, to maintain a definite temperature in the body, or whether it is to be looked upon solely as a waste product

arising incidental to the metabolism occasioned by other physiological functions like muscular and glandular activity, is still a debated question. The temperature of man being approximately uniform, obviously changes in the thermal environment must affect the rate of dissipation of heat from the body or its production, or both. Changes in metabolism must thereby arise. Voit attempted to ascertain the extent of such changes by measuring the carbon dioxide production in a man of 70 kilograms body weight kept at different temperatures. The figures (per hour) found are given here:

Temperature.	CO ₂ in Grams.
4.5° C.	35.1
6.5° C.	34.3
9.0° C.	32.0
14.3° C.	25.8
16.2° C.	26.4
23.7° C.	27.4
24.2° C.	27.6
26.7° C.	26.6
30.0° C.	28.3

It will be observed that a "regulation" of metabolism in the sense of increased metabolism takes place only at the lower temperatures. At higher ranges, a "physical" regulation takes the place of the "chemical" or metabolic adaptation. At lower temperatures, it is by no means unlikely that the demand for heat is satisfied by direct combustion of body material—that is, a metabolism of energy—whereas at ordinary temperatures, the heat liberated in connection with the usual metabolic changes more than suffices to maintain the body temperature. The evidence seems favorable to the idea that, ordinarily, heat production is incidental to the metabolic processes and is sufficient to maintain the temperature of the individual above that of his surroundings. Whatever excess of heat may be produced is got rid of in various ways; for there is no evidence of diminished metabolism (and diminished generation of heat) with increase of external temperature. Heat is produced in excess. On the other hand, when external conditions are given in which this excess changes to a deficit, metabolic processes are provoked. At low temperature, accordingly, a "chemical" regulation is inaugurated, not through direct intermediation of the food, but by increased protoplasmic activity.

The removal of the "waste heat" of metabolism is affected by a number of factors, such as the condition of the atmosphere, insolation, relative humidity, etc., which are subject to great variations. As Rubner pointed out, the process of civilization has tended to eliminate, moderate, or equalize to some degree these external changes. There has thereby resulted a disposition on the part of the body of civilized man to lose some of the regulatory responses which primitively belong to him. The maintenance of heat equilibrium in relation to the mass of tissue involved and the size of the surface exposed—variations corresponding to large and small individuals—is apparently due to a nice adjustment of metabolism.

FOOD UTILIZATION OR AVAILABILITY

That the feces contain residues of undigested food is easily shown. It is apparent that if the ingested food was *completely* digested, absorbed and utilized there would be no need for a discussion of food "utilization" or "availability." However, the ordinary diet is such that the nutrient materials are in part either undigested or indigestible and for this reason represent an actual loss of energy to the body. At one time it was believed that the nitrogen of the feces represented the portion of the ingested nitrogenous material which had not been utilized by the body, but the nitrogen of the feces is made up not only of such material, but of bacteria, epithelial cells and residues of digestive juices. The nitrogen exclusive of that due to food residues (and a portion of the bacterial nitrogen) is now classed as *metabolic product nitrogen*. In calculating the actual utilization or availability of an ingested protein food we must therefore subtract the metabolic product nitrogen from the *total* nitrogen of the feces to learn what part of the ingested nitrogen has actually been lost to the organism.

On the basis of data collected from a large number of experiments carried out under the auspices of the United States Department of Agriculture, Atwater calculated coefficients of availability for the various nutrients of the ordinary mixed diet as follows: Protein, 92 per cent.; fats, 95 per cent.; carbohydrates, 97 per cent. In the infant organism from 91 to 94 per cent. of the total nutrients ingested have been found to be utilized (Rubner and Heubner).

The most important and practical utilization studies have concerned the protein foods. Müller in experiments on dogs fed nothing but meat found over 98 per cent. of the nitrogen of the diet was utilized. Prausnitz determined the utilization value of *fresh* meat to be 93 per cent. and *dried* meat 90 per cent. As the percentage of nitrogen in the feces from the dried meat diet was higher than that from the fresh meat diet it seems likely that some of the dried meat was not absorbed. Forster found that 91 to 96 per cent. of meat powder nitrogen was utilized. Mendel and Fine secured a utilization factor of 94 per cent. for fresh meat and slightly over 90 per cent. for meat powder.

Mendel and Fine also demonstrated the influence of *indigestible non-nitrogenous materials* upon the fecal nitrogen. They found that the fecal nitrogen was increased from 60 to 192 per cent. by the addition of from 6 to 13 grams of such materials (agar-agar and bone ash). This increase in fecal nitrogen is due to stimulated peristalsis which has caused a larger quota of metabolic products to escape absorption. These data emphasize the necessity of making a correction for metabolic product nitrogen before calculating the actual utilization of the ingested nitrogen. In making this calculation it is simply necessary to subtract the metabolic product nitrogen from the *total* nitrogen of the feces and divide the remainder by the ingested nitrogen, all values expressed in grams. It is obviously never safe to judge of the availability, digestibility, or utilization of an ingested food on the basis of the *percentage*

of *nitrogen* in the stool. Mendel and Fine give data (corrected for metabolic product nitrogen) which indicate meat as 100 per cent. utilized. It is no doubt true, as they state, that feces resulting from a meat diet "are for the most part of metabolic origin." However, we are inclined to believe that meat is never completely utilized. Careful microscopic examination of the stool will demonstrate this in most instances. We can readily appreciate that there might possibly be complete utilization of carbohydrates under certain circumstances, but are strongly inclined to believe that such a condition does not hold for ingested protein. In cases of food "bolting" and "Fletcherizing" the following utilization values have been determined for meat by Foster and Hawk (values corrected for metabolic product nitrogen): Bolting, 95.6 per cent.; Fletcherizing, 97.4 per cent.

Many investigations of the relative availability of vegetable foods have been made. Atwater and Bryant rate the availability of vegetable foods (84 per cent.) far below that of animal foods (97 per cent.). Recent experiments, however, show that the individual proteins present in wheat, for example, "are as thoroughly utilized as the nitrogenous components of fresh meat" (Mendel and Fine). In the interpretation of utilization values from vegetable sources we must remember that the protein in its native form, *i. e.*, accompanied by its associated non-nitrogenous, non-digestible material, is less thoroughly digested and absorbed than the same protein when fed in the form of the pure product.

The values as given by Atwater and Bryant represent the former condition, whereas those of Mendel and Fine represent the latter. Constantinidi found gluten to be 94 per cent. utilized by man and 97 per cent. by dogs. Lusk (87 per cent.), Kornauth (91 per cent.), and Potthast (92 per cent.) have found a somewhat lower availability for the wheat product. Abderhalden found gliadin to be 94 to 98 per cent. utilized. Michaud reports the utilization of "glidine" as ranging from 86 to 96 per cent., whereas Buslik and Goldhaber report tests showing this preparation to be as thoroughly utilized as meat. In recent experiments made in the writer's laboratory (Howe and Hawk) it was demonstrated that meat and glidine were equally well utilized (97 per cent., uncorrected for metabolic nitrogen); gluten was less available (86 to 90.5 per cent.). The fact that utilization values are not necessarily reliable indexes of the relative nutritional efficiency of foods is demonstrated in the data from the meat and glidine tests referred to above. The protein from these two sources was equally well utilized. However, when we examine the nitrogen balances we observe that the meat yielded a *plus* nitrogen balance of 11.3 grams, whereas glidine gave a *minus* balance of 1.3 grams. It is evident, therefore, that so far as digestion and absorption are concerned there is apparently no margin of choice between meat and glidine. However, when the question of the retention of their nitrogen for the use of the organism is concerned the evidence is strongly in favor of meat.

So far as *bread* is concerned the most recent experiments (Newman, Robinson, Halnan and Neville, and others) indicate that "there is no justification for extreme views as to the advantage or disadvantage

possessed by different kinds of bread of the commoner types at any rate as regards the availability." The various kinds of flour are all *economical foods*. Recent experiments indicate that we may rate the breads as to availability of energy and protein constituents as follows:

Kind of bread.	Availability of	
	Protein.	Energy.
Graham	81 per cent.	83 per cent.
Whole wheat	83 "	87 "
Standard (white)	89 "	91 "

The utilization of *corn* is of great practical importance, and the earlier utilization tests indicated rather a low availability. Rubner reported that *polenta* (an Italian preparation of corn and cheese) is 80 per cent. utilized, and Albertoni and Novi, and Erismann have verified this. Merrill reports the utilization of corn nitrogen as ranging from 61 per cent. to 86 per cent., and Grandeau with horses found an availability of only 69 per cent. This latter finding is of particular significance because of the great length of the intestine of the horse and the comparatively prolonged activity of the cellulose-dissolving bacteria. Very few tests have been made in which the proteins of corn have been isolated and fed. The most important protein of corn is *zein*, an alcohol-soluble protein which constitutes about 50 per cent. of the total protein of corn. Rockwood demonstrated a utilization value of 78 to 90 per cent. for this protein. The studies of Mendel and Fine, on the other hand, lead to the conclusion that the corn proteins (partially purified and fed as corn gluten) are only slightly less available than meat proteins. In fact in certain experiments in which meat was fed, accompanied by a quota of non-digestible, non-nitrogenous materials (agar-agar and bone ash) comparable to the non-nitrogenous materials present in the corn gluten, the above authors demonstrated that the corn nitrogen was about as thoroughly utilized as was the meat nitrogen.

The utilization of the nitrogen of cotton-seed flour has been found by Mendel and Fine to be 67 to 75 per cent., whereas "meat diets containing comparable or greater amounts of indigestible materials" were 88 to 93 per cent. utilized. Fraps had earlier reported the protein of cotton-seed as 88 per cent. available. However, he used steers and sheep as experimental animals, whereas dogs were used in the other investigation. One would reasonably expect a higher utilization value in the case of the herbivora. Mendel and Fine also reported results on the utilization of legume proteins. They say: "In comparison with the other vegetable proteins thus far reported in this series of studies, the legume proteins are less well utilized. The materials investigated principally were (1) soy bean flour, free from starch; (2) a product prepared from the white bean by thoroughly disintegrating the cells and dissolving and washing out the starch; (3) phaseolin—a protein isolated from the white bean; and (4) an uncoagulated globulin from the garden pea. The unfavorable results with the soy bean and white bean preparations can be explained only in part by the presence of cellulose and hemicellulose in the products. Such considerations cannot

be applied to the data for phaseolin and pea globulin." Earlier experiments are unanimous in according a low utilization to legume nitrogen.

Practical dietetics has long had to contend with a conflict of opinions regarding the true nutritive value of many familiar food materials. The errors are associated with exaggerated or incorrect ideas regarding the food value of specific dietary articles; and a prejudice against food materials of certain origin has been fostered in the absence of accurate scientific testimony. Current notions regarding the relative value of different kinds of bread furnish an illustration. Wheat or rye flour is used most extensively, though some kinds of bread are prepared from barley or maize. The oat will not yield a light porous bread. Further differences are brought about by the choice of leavening agent used.

In the manufacture of the commonly used "patent" wheat flour by the modern process of milling, the bran and aleurone layers, together with the germ, are removed by preliminary treatment and the remainder of the kernel is then ground. The bran, if included, would make the flour coarse; the germ is removed because it contains oil, which acts upon the other constituents of the flour so that the bread in baking is darkened in color. The portions removed by the processes of refining are characterized especially by their richness in nitrogenous materials and inorganic salts. There has been much controversy regarding the nutritive value of the bran; and it has been claimed that valuable parts of the wheat are left in the waste cortical portions. To avoid this loss Graham flour is prepared by grinding the whole of the wheat kernel; and since no bolting or sorting process is introduced the product is in reality a wheat meal. As an intermediate product between the coarse Graham flour and the finest products, the so-called "whole wheat" or "entire wheat" flour has arisen. In this the attempt is made to remove only the woody part of the bran, leaving the aleurone layer and the germ with their nitrogenous and other ingredients.

Experimental observations now recorded in large numbers indicate how unreliable chemical analysis alone may be in determining the relative nutritive value of the different breads made from many kinds of flour. Actual trials on man show that wheat bread is more completely utilized than rye bread. Bread prepared from wheat flour is absorbed from the alimentary tract in larger or smaller amount according to the fineness of the flour used, the finest behaving most favorably in this respect. When the flour is prepared from the whole grain there is always a considerably larger residue of unutilized food. Judging from the relatively large residuum of undigested material left after ingestion of the coarser kinds of bread, especially those containing considerable bran, the compounds included therein are protected from the digestive juices by their environment of cellulose and other indigestible substance and thus fail to contribute the food value which their composition discloses.

Experience accumulated in comparing the availability of proteins obtained from vegetable sources with those furnished by animal tissues has led to the inquiry whether these different types of proteins exhibit inherent differences in real digestibility. Not a few writers have assumed this to be the case. But observations made in various laboratories

give no support to this view. Oat protein, for example, isolated and purified was found no less readily utilized than that from lean meat or milk; and this corresponds with similar experience with other vegetable proteins. When, however, they are still mixed with the materials naturally associated with them, vegetable proteins are not ordinarily utilized to the same extent as those of animal origin. In distinction from cereals and legumes, "vegetables," such as cabbage, beets, etc., are of little value as sources of protein or fat, although the carbohydrates which they contain appear to be quite well digested and absorbed.

There is a prevalent opinion that mushrooms or edible fungi constitute a usually acceptable article of diet. It has been stated that mushrooms may contain 20 to 50 per cent. of protein material in their dry matter and suggested that such material might properly be termed "vegetable meat" and used as a substitute for animal food. It is true that mushrooms do contain a high content of nitrogen, but much of this is non-protein. Mendel showed that the familiar edible mushrooms contain very large quantities of nitrogenous carbohydrates which resist digestive changes and are not available to the organism. He emphasized the fact that while edible fungi may properly be regarded as dietetic accessories, they ought by no means to be ranked with essential foods.

By certain experiments (Mattill and Hawk) in the writer's laboratory it was determined that "the ingestion of large amounts (1000 cc.) of water with meals caused the protein constituents of the food to be more completely utilized, as shown by a decrease in all forms of nitrogen in the feces."

The ordinary *soluble* carbohydrates are utilized to a high degree by the animal organism. When fed in proper quantities (which do not exceed the assimilation limit) we may say that soluble carbohydrates or carbohydrates which are changed into soluble forms in the intestine (*e. g.*, starch) are at least 97 per cent. utilized by man. Many experiments have been made upon cellulose utilization, but there are still varying opinions in the matter. That cellulose is better utilized in the herbivorous organism than in the human or carnivorous organism has been established. This is no doubt facilitated by the presence of bacteria possessing the power of dissolving this complex carbohydrate. The actual utilization values are placed at 25 per cent. for herbivora, less than 5 per cent. for dogs, whereas the utilization by man is "too small for it to play a rôle of importance in the diet of a normal individual" (Swartz). Experiments by Lusk and others have indicated that there is probably no formation of glycogen or sugar from ingested cellulose. Tappeiner believes that the cellulose which is utilized (or which at least disappears from the intestine) is principally changed into acids of the fatty acid series.

Of the hemicelluloses, pentosans (gum arabic, etc.), according to Swartz, are 40 to 80 per cent. utilized by herbivorous animals. Very few records are available as to utilization by the human organism, but the data indicate that 80 to 95 per cent. of the ingested pentosans disappear from the intestine (König and Reinhardt). Bacteria are believed to be actively interested in this hemicellulose transformation (Cramer).

The pentosans are of secondary importance in human nutrition because of the fact that they are probably not glycogen-formers.

Of the second class of hemicelluloses, the galactans, agar-agar is probably the most important. Saiki has demonstrated that this galactan has a utilization factor of 8 to 27 per cent. in man. A utilization of 50 per cent. has been demonstrated for herbivora (Lohrseh).

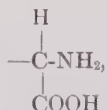
Many of the recorded data regarding *fat utilization* are unreliable because of defects in the method of feces analysis. The older procedure of ether extraction removed lecithin, cholesterol, etc., and caused these substances to be reckoned as fat. Modern methods eliminate these inaccuracies. It is probable that ingested fat is at least 95 per cent. utilized by the normal human organism when the quantity ingested is kept within reasonable bounds (under 100 grams per day). When the fat ingestion is excessive the utilization will be less satisfactory. The character of the ingested fat also influences its actual utilization, the fats of low melting points apparently being somewhat better utilized than those of higher melting points.

PROTEIN METABOLISM

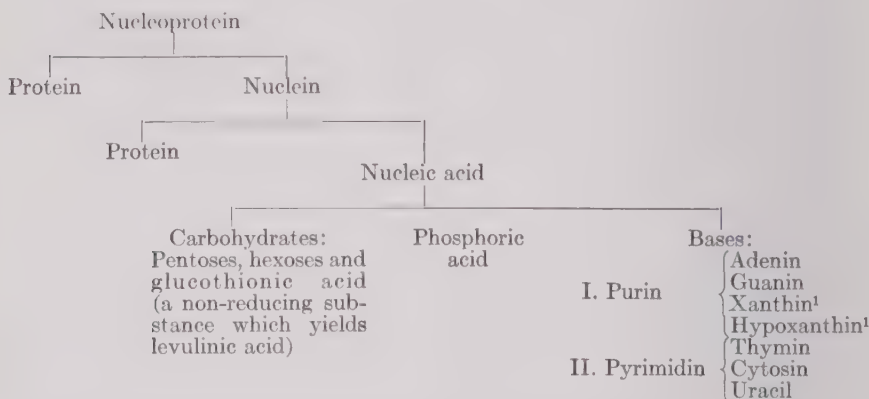
Characteristic products of protein katabolism are found in predominant quantity in the urine, although the feces and sweat also contain part of the nitrogenous waste. In addition to urea, creatin, creatinin, uric acid and other purin derivatives, hippuric acid, and ammonium salts, a few others occur in quantities which are normally very small but may be largely increased when metabolism is disordered. The sulphuric and phosphoric acids eliminated in combination with various bases are also for the most part referable in origin to the proteins which contain sulphur and phosphorus. The chemical nature of the nitrogenous metabolic products which escape with the stools is scarcely known; the small portions lost with the sweat are allied closely to those found in the urine.

In following the transformations of proteins in the organism, it is necessary to bear in mind that they represent a great group of foodstuffs varied in physical characters and chemical behavior, yet essentially allied in structure insofar as they yield similar decomposition products. The latter are generally comparable, whether produced by hydrolysis with acids or by cleavage with proteolytic enzymes. The simpler types of protein subjected to such decomposition yield leucin, glycocoll, α -amino-valerianic acid, alanin, aspartic acid, glutamic acid, serin, cystin, tyrosin, phenylalanin, pyrrolidin, carbonic acid (prolin), oxypyrrolidin, carbonic acid, lysin, arginin, histidin, tryptophan, and ammonia.

The individual groups of proteins differ in the proportions of these different derivatives and future investigation will doubtless afford additions. From the chemical standpoint, it will be noted that the products thus far obtained are for the most part amino-acids or similar compounds, a preponderance of NH_2 groups in some of them giving a decidedly basic character to the molecule. The conspicuous feature of the structure of all these derivatives is the presence of the group—



and Fischer has shown that such groups are prone to form continuous syntheses in which the carboxyl group of one becomes united with the amino group of another. This explains the characteristic cleavage of the proteins into α -amino-acids and their corresponding behavior toward enzymes as well as their characteristic deportment like acids and bases simultaneously. The sulphur is largely, if not entirely, grouped in the form represented in the cleavage product, cystin; and this throws light upon the origin of the cystin which is excreted in the rare metabolic disturbance connected with cystinuria. Many proteins apparently contain a carbohydrate group; but the typical carbohydrate derivatives obtained from the compound proteins like the mucoids are now recognized as amino-sugars, of which glucosamine is the most common. Other proteins, like the vitellin of egg-yolk and casein of milk, contain phosphorus in radicals not yet recognized by the chemist. This element plays an important part in nutrition, and the phosphorized proteins are thus responsible in no small degree for the phosphates eliminated. In nucleoproteins, the presence of the nuclei-acid group introduces a new series of complexes which have a significant rôle. The following scheme indicates the course of nucleoprotein decomposition:



The ferruginous proteins like hemoglobin, as well as the albuminoids (scleroproteins) keratin, elastin, etc.—all offer specific differences. Enough has been indicated to make clear the possibility of very different nitrogenous transformations, in accord with the varying complexity and chemical make-up of the specific proteins attacked.

When we attempt to follow the fate of ingested proteins we are confronted with the query as to just how far they are changed in the intestine previous to absorption. Inasmuch as proteoses and peptones

¹ Formed in a secondary reaction from adenin and guanin.

were formed in the intestine by digestive alterations, and since these were not present in the blood, it was at one time assumed that the blood proteins were synthesized from these proteoses and peptones during their passage through the intestinal wall. Later it was demonstrated that the final products of intestinal digestion were not proteoses, peptones and peptides, but *amino-acids*, these final products of protein cleavage being formed through the joint action of the enzymes, trypsin and erepsin. We were unable to demonstrate the presence of amino-acids in the blood and were compelled to fall back upon the synthetic power of the intestinal mucosa to account for the blood proteins. That this hypothesis, seemingly well-founded, was not accepted as final by all nutrition workers is evidenced by the following prophetic words of two celebrated physiological chemists: "It is by no means certain that only 'regenerated' protein reaches the blood current from the intestinal sources; and it may be found that the quantities of cleavage products absorbed at ordinary intervals escape detection by the methods now available" (Chittenden and Mendel).

That these words of Chittenden and Mendel were truly prophetic has only very recently been demonstrated. After the refinement of method, suggested as necessary in the above quotation, had been made, Folin and Denis, and Van Slyke and Meyer, and others succeeded in demonstrating the presence of *amino-acids in the circulating blood*. Van Slyke and Meyer have gone further and determined the actual concentration of these amino-acids in the tissues. On the basis of the various experiments it now seems that the greater part at least of the amino-acids which are formed in the intestine as a result of protein digestive cleavage are passed into the blood stream *unchanged* and carried to the various tissues and organs of the body and here deposited. Later the stored amino-acids are utilized for tissue construction as needed. The surplus acids are deaminized, the carbonaceous portion burned, and the NH_2 groups utilized in the production of urea. According to this theory, then, we may have urea formed in *all tissues*. Folin believes that the major part of the urea is formed *in the muscles* because this type of tissue predominates, whereas Van Slyke and Meyer claim to have demonstrated that the liver and kidney are more active than the other organs in urea formation. That amino-acids are stored in the tissues is shown by the fact that the concentration of amino-acids in the tissues is approximately *ten times* as great as that of the blood.

According to our former view the deamination process was believed to be localized in the small intestine and the ammonia of the portal blood was believed to originate in this way. Very recently Folin and Denis have shown that the portal ammonia does not arise from the intestinal deamination of amino-acids, but has its origin in *putrefaction processes* which take place in the *large* intestine. The significance of portal ammonia is therefore widely altered.

We have pointed out the conspicuous behavior of the proteins in their failure, under ordinary conditions, to be retained. The elimination of nitrogen begins to increase almost immediately after a meal rich in proteins. Experiments by Sherman and Hawk illustrate the character

of this response. When lean beef sufficient to furnish about 64 grams of extra protein was taken with breakfast, the nitrogen in the urine began to rise in the first three hours and reached a maximum between the sixth and ninth hours, after which it declined at first rapidly and then more slowly. The increased excretion of sulphates was proportional to that of the nitrogen and followed the same general course. The increased heat of combustion of the urine was but little greater than would correspond to an amount of urea equivalent to the extra nitrogen eliminated. The other constituents of the urine were therefore but little affected, and a moderate gain or loss of body nitrogen did not seem to affect the changes noted. Cathcart and Green have reported data which indicate that the sulphur portion of ingested protein is katabolized more rapidly than the nitrogen.

Falta has observed that after the ingestion of equal quantities of nitrogen in the form of different protein substances such as egg albumen, casein, gelatin, etc., the *rate* at which nitrogenous equilibrium is again established varies with the materials used. It is not improbable that these differences in rapidity of katabolism are ascribable to an unlike resistance of the proteins to the alimentary digestive processes, which accordingly alters their rate of absorption.

Influence of Proteins on Metabolism.—The unique importance of proteins in nutrition, owing to their content of nitrogen in proper form, has already been mentioned. Since the body is unable to utilize extensively other types of nitrogenous compounds in the entire absence of true proteins, except the immediate decomposition products of the latter (amino-acids), prolonged protein hunger becomes as serious in its consequences as does the complete absence of food. Under suitable conditions a carnivorous animal like the dog can be kept in nutritive equilibrium on an exclusive meat diet. To accomplish this the animal must eat three to four times as much protein as is decomposed during hunger. It has thus far been impossible to maintain similar equilibrium in man on an exclusive protein diet. The failure to do so is associated, in part at least, with the inability to digest properly the enormous quantities requisite. The net available energy of the proteins is smaller than their heat of combustion would indicate, owing to the incompletely oxidized products which are liberated from them. The digestive work which they entail is also not inconsiderable. Every increase in the amount of protein fed tends to increase the katabolism of protein. By virtue of the tendency of the body to adapt its nitrogenous katabolism to the protein intake, it becomes possible to attain nitrogenous equilibrium with widely varying quantities of protein. In all of these cases it is understood that the total intake of food must be sufficient to cover the demands of the body for energy. In the fasting condition the latter may amount, in the case of a man of average body weight, to somewhat over 2000 calories per day, or 30 large calories per kilo of body weight. When food is taken, and no external work of any consequence is performed, the metabolism of energy is slightly increased over the fasting figure, perhaps to 32 or 33 large calories per kilo per day; while under conditions of muscular activity the demand for energy may

be increased under extraordinary circumstances to 100 large calories per kilo per day or over.

Provided that these nutritive demands are satisfied, the absolute quantity of protein required to prevent a loss of body protein will depend somewhat on the proportion of non-protein foods ingested and absorbed. A determination of the maximum quantity of protein which can be utilized is scarcely feasible in the case of man, since it is practically impossible to exceed 200 grams in the intake without eliciting unpleasant symptoms. While it is true that most experiments in this direction have been carried out with meat as the chief source of the protein, and that the extractive substances (such as lactic-acid salts, creatin, potassium salts, etc.) cannot be regarded as physiologically inert and non-toxic, yet there is no reason to believe that larger quantities of pure proteins of animal or vegetable origin should be consumed with relish for any length of time. It is unlikely that a nutritive equilibrium could ever be established in man on an exclusive protein diet.

While an increase of the proteins in the diet tends to augment protein katabolism and leads to a greater elimination of nitrogen in proportion to the supply of proteins offered, an increase in the fat or carbohydrate constituents of the food tends to diminish protein katabolism, although the latter cannot be completely stopped under any combination of diets. An animal which receives a nitrogen-free diet of either fat or carbohydrate or both, will not succumb as soon as a starving animal. Nevertheless, the continued nitrogen losses during nitrogen (or protein) hunger lead to a fatal result as inevitably as does complete inanition. More recent work has shown that in protein starvation the loss of body protein may become far smaller than the earlier investigators found. The essential feature in maintaining a lower plane of protein metabolism in these cases consists in the administration of sufficient non-protein nutrients to cover more nearly the demands of the organism for energy. This is well illustrated in experiments made by Folin on man. On a diet consisting of 400 grams of pure arrow-root starch and 300 cc. of cream containing 15 to 25 per cent. of fat, together with a few grams of salt, the daily output of nitrogen was reduced to between three and four grams in all the individuals under observation over a period of several days. This effect appears to be common to both fats and carbohydrates, although in different degree.

Effects of Non-nitrogenous Nutrients on Protein Metabolism.—The effect of carbohydrate and fat on the metabolism of proteins under conditions in which the total nutritive demands are more nearly satisfied is deserving of closer attention. Although these non-nitrogenous nutrients cannot check the katabolism of body protein in protein hunger, they are capable of exerting a definite and important influence in diminishing the extent of protein katabolism. This is usually spoken of as the *protein-sparing* action of fats and carbohydrates. The following experiment by von Noorden and Dieters illustrates the protein-sparing action of carbohydrates in man. The daily nitrogen intake during a period of four days amounted to 12.6 grams, with a daily output, in the urine, of 10.4 grams of nitrogen. When, on the fifth day, 200 grams

of cane-sugar were added to the diet the urinary nitrogen fell to 9 grams. According to this, 1.4 grams of nitrogen (equivalent to 13 per cent. of the previous output) had been spared in the form of protein. Similar protein-sparing effects have been obtained with fat. The experience of all observers agrees in indicating the superiority of carbohydrates over fats in this respect. Voit found an average decrease in protein metabolism of about 7 per cent. with fats and about 9 per cent. with carbohydrates. It should be noted that possible differences in the relative availability of the supposedly "isodynamic" quantities of fat and carbohydrate have not been drawn into consideration by most investigators.

Marked differences in the rôle of the fats and carbohydrates of the food in sparing body-fat have not been made out. Armsby has summarized the range of choice by the organism and the mutual replacement of nutrients. "The amount of protein material necessarily required for the metabolism of the mature animal, we have seen to be relatively small. Aside from this minimum, the metabolic activities of the body may be supported, now at the expense of the body-fat, and again by the proteins, the fats, or the carbohydrates of the food. Whatever may be true economically, physiologically the welfare of the mature animal is not conditioned upon any fixed relation between the classes of nutrients in its food supply, apart from the minimum requirement for proteins."

Among the non-nitrogenous ingesta, cellulose, owing to its indigestibility, plays little if any part, further than to increase the nitrogenous waste leaving the body when large portions of indigestible foods are fed. The few data available on the action of pentoses—the five-carbon sugars like arabinose, xylose, and rhamnose—upon protein metabolism disclose no marked effects. The fatty acids have been found to exert a protein-sparing influence quite comparable with that of the fats from which they are derived; while the remaining component of the latter, the glycerol, appears to be negligible in this regard when equivalent doses are used.

Influence of Alcohol, Gelatin, etc., on Protein Metabolism.—The views regarding the value of alcohol as a food and its influence on metabolism are somewhat divergent, and some of the testimony has not always been free from bias. That it is in large measure burned in the body seems reasonably certain, at least as far as this applies to moderate quantities. We must, however, distinguish carefully between large doses which have an unmistakable toxic action, and smaller doses in which the alcohol appears to exert a protective action on protein and fat. In careful metabolism experiments by Atwater and Benedict, results with ordinary diet were compared with those in which part of the fats and carbohydrates of the food were replaced by the isodynamic amount, about 72 grams ($2\frac{1}{2}$ ounces), of absolute alcohol. This is about as much as would be supplied in a bottle of claret or 6 ounces of whisky. The quantities of alcohol eliminated by the lungs, skin, and kidneys, varied from 0.7 to 2.7 grams, and averaged 1.3 grams per day. Over 98 per cent. of the ingested alcohol was oxidized in the body, and one gram of alcohol was calculated to be isodynamic with 1.73 grams carbohydrate

or 0.78 gram of fats of ordinary food materials. The proportions of food and of the several kinds of nutrients made available for use in the body were practically the same in the experiments with and those without alcohol in the diet. The potential energy of the alcohol was transformed into kinetic energy in the body as completely as that of ordinary nutrients. The efficiency of alcohol in the protection of body fat from consumption was very evident, but in protecting body protein was not fully equal to the isodynamic amounts of the ordinary nutrients, the result depending somewhat on the extent to which the individual was accustomed to the use of alcohol. We may repeat with Atwater and Benedict, "that there is a very essential difference between the transformation of the potential energy of the alcohol into the kinetic energy of heat, or of either internal or external muscular work, and the usefulness or harmfulness of alcohol as a part of ordinary diet."

It would be a mistake to assume that alcohol can be rated as a true non-nitrogenous food in the sense in which fats and carbohydrates are foods. For experiments have shown that alcohol prior to its combustion in the body exerts a noticeable influence upon the metabolic processes in the liver, and possibly in other organs, whereby a marked effect is produced upon the output of uric acid. Alcohol, and especially alcoholic drinks, when taken with purin-containing foodstuffs, exert a direct influence upon the metabolism of those compounds which give rise to exogenous uric acid, increasing largely the amount of uric acid excreted (Beebe). Whisky, for example, may be given with impunity when the patient—as in typhoid fever—is on a light or purin-free diet, without materially influencing the production or output of uric acid; but when the alcoholic fluid is taken with a hearty meat diet, or with any diet containing free or combined purin compounds, the system is at once liable to show the effects of the excess of uric acid.

It is appropriate to consider the influence exerted upon metabolism by a number of substances which cannot properly be classed among the typical foodstuffs, but nevertheless may enter to an important extent into the make-up of the diet. Among the nitrogenous compounds, *gelatin* stands foremost. Although closely related to the true proteins, gelatin is sufficiently characteristic and peculiar in its chemical make-up to be classed in the group of albuminoids (proteoids, scleroproteins). Experiments on man and animals have demonstrated the failure of gelatin to prevent loss of body protein when it is the sole nitrogenous compound fed. It can replace protein to a very large extent, and it acts conspicuously in sparing both protein and fat in the body. In the absence of other forms of nitrogenous substances, animals fed on gelatin with non-nitrogenous nutrients succumb within a few weeks. Experimental data obtained on animals by C. Voit and by I. Munk show that 100 grams of gelatin will protect about the same quantity of protein as is spared by 200 grams of carbohydrate. Body-fat can be protected by gelatin feeding. The gelatinous tissues (tendons and cartilage) exert a similar protein- and fat-sparing action to the extent to which they are digested and converted into gelatin in the alimentary tract.

The literature abounds in studies regarding the influence of a large

variety of substances, both organic and inorganic, upon metabolism. Some of these, like the drugs, cannot be considered here; others, like tea, coffee, and various dietary accessories, exert no profound action on the organism in moderate dietetic quantities. In recent years food preservatives, such as borax and boric acid, sulphites, benzoic and salicylic acids, formaldehyde and fluorides, have received special consideration in view of their increasing and widespread use. At the present time it would be unprofitable to generalize from these studies.

The Intermediary Metabolism of Proteins.—This remains a most obscure chapter and the progress of physiological chemistry has helped to make the subject more complex. Thus in speaking of the albuminous substances we are now prepared to distinguish between the various members of a great group of organic compounds related in many chemical and physical features and yet sufficiently different in structure and physiological behavior to demand a special interpretation for their rôle in metabolism in many instances. In this way, for example, a familiarity with the specific metabolism of the nucleoproteins, with their phosphorus, carbohydrate, purin, and pyrimidin complexes, has been obtained; and little by little the independent origin of the different nitrogenous excretives has been unravelled. The source of the katabolites, urea, uric acid, and oxalic acid, has been traced to different members of the protein family; whereas at one time they were attributed to a common source which was assumed to give rise to diverse end products by obscure variations in the metabolic processes of the organism, now yielding one, now another of them. Similarly, the physiologist is able to distinguish between the metabolic fate of proteins which convey phosphorus to the organism and those which do not; or, looking from another point of view, to refer eliminated phosphorus to a variety of possible origins—the phosphates ingested, or the phosphorus of gland nucleoproteins, lecithins, or disintegrating leukocytes, as the circumstances may direct. In this way he aims to obtain a deeper insight into the chain of events which constitute intermediary metabolism—what Foster has termed the “gaps and guesses” of nutrition. There is so much which is uncertain and the subject of controversy that we shall aim to recount briefly only such facts and theories as have received more general acceptance, or are deserving of special recognition.

If we follow more closely the history of the various nitrogenous urinary constituents we shall find that they represent quite distinct processes in intermediary metabolism. The urea output, in proportion to the total nitrogen elimination, may be greatly diminished in disease. The experiments of Folin make it probable that even in health the urea fraction of the nitrogenous excretives may be very greatly reduced when the minimum proteins requirement of the organism is not overstepped.

Urea.—Up to very recently the view most generally held as to the formation of urea was briefly as follows: Ingested protein material is digested by the proteolytic enzymes of the intestine with various amino-acids as the ultimate cleavage products. Such portion of these amino-acids as are needed for the construction of tissue protein are synthesized in their passage through the walls of the intestine and appear in the

circulation as blood protein. This blood protein is then carried to the tissues where it is reduced to the form of amino-acids and the tissue cells build their own characteristic protein from these acids (Abderhalden). Such of the intestinal amino-acids as are not needed for the manufacture of blood proteins are *deaminized* (NH_2 groups split off). These *amino* groups are then transformed into ammonia and this ammonia, in the presence of carbon dioxide, yields ammonium carbonate. This ammonium carbonate is then carried to the liver in the portal circulation and the hepatic cells transform it into urea, thus:



The non-nitrogenous part of the original amino-acid is then utilized as a source of energy.

Very recently certain very important experiments (Folin and Denis; Buglia; Van Slyke and Meyer and others) have cast grave doubt upon the accuracy of the long established view. It seems that amino-acids are present in the blood. Folin and Denis claim that "The food protein reaches the tissues in the form of amino-acids and those amino-acids which are not needed for the rebuilding of broken down body material are not rebuilt either into protein or protoplasm, but are broken down and their nitrogen converted into urea. . . . The muscles and other tissues as well evidently serve as a storehouse for such reserve materials. . . . The urea-forming process is one characteristic of *all the tissues* and by far the greatest amount of the urea is therefore probably formed in the muscles."

In line with the above Buglia has found that only a small part of the amino-acid introduced intravenously is excreted. Van Slyke and Meyer have verified and expanded the findings of Folin and Denis. They have made a *positive* demonstration of amino-acid nitrogen in the blood and have further, by direct tissue analysis, demonstrated a concentration of these amino-acids in various tissues. They state that such tissues as muscle, liver, kidney, spleen, and pancreas contain about *ten times the amount of amino-acid nitrogen* per 100 grams that is found in the blood. Their investigations show conclusively that the amino-acids absorbed during digestion are immediately taken up by the tissues. Van Slyke says: "Experiments seemed to show that while the muscles are stored with amino-acids up to their saturation point after a heavy feeding of meat, the liver and kidneys metabolize their portion of the products as rapidly as they receive them. . . . The disappearance of the amino-acids from the liver and kidneys was accompanied by an increase in the urea content of the blood. These facts strengthen the view that the liver is active in transforming the products of protein digestion into urea." The amino-acids are believed to be held in the tissues by absorption and the chemical transformation of the absorbed acids is believed to follow.

Matthews and Miller, as the result of experiments upon animals equipped with the Eck fistula, offer the following "speculation:" "The liver does not form urea from ammonia or ammonium compounds when presented to it in the arterial blood, but when the liver ceases to be a

factor in the formation of urea, the other tissues of the body gradually assume the work in this regard, normally done by the liver. This is paramount to saying that no specific tissue of the body enjoys the sole monopoly to form urea in the process of nitrogen metabolism, but that urea is formed by the tissues in general, at least primarily; and that after the removal of certain specialized tissues (organs) which possess this power to a greater degree than the general tissue, there follows a reversion to the original form of metabolism by the tissues in general which may be sufficient to maintain the nutrition of the body without the intervention of specialized tissue."

It is a noteworthy fact that in none of the experiments on the assimilation of protein digestion products, has the *possible* synthesis of a *part* of the amino-acids into blood protein in the wall of the intestine been disproved.

In certain diseases, especially such as seriously involve the functions of the liver, the proportion of urea nitrogen eliminated may diminish very markedly, falling even below 10 per cent. of the total output. In some instances this may be due to the small intake of protein and corresponding diminution of exogenous protein metabolism. But as the output of ammonia is almost always very large in these cases, amounting at times to 40 per cent. of the entire nitrogen output, it is more likely that the formation of acid products in intermediary metabolism—the condition known as acidosis—may draw upon the ammonia for purposes of neutralization. For this reason, the elimination of ammonia is increased by administration of mineral acids; and under such conditions and in such diseases as in fevers and diabetes, where an increased formation of acid takes place, the quantity of ammonia in the urine is increased. The ammonia may be afforded by additional protein katabolism and the destructive removal of fixed alkali thus prevented. The absolute quantity of ammonia eliminated ordinarily is small—approximately one-half gram per day.

Ammonia.—Normally from 2.5 to 4.5 per cent. of the total nitrogen of the urine is eliminated in the form of ammonia. The actual excretion aggregates about 0.7 gram per day. The ammonia is present for the most part as the chloride, phosphate or sulphate. Following the administration of ammonium salts of the mineral acids or of the acids themselves there is an increased output of ammonia, due to the fact that these *inorganic* ammonium salts are not oxidized in the organism to form urea. On the other hand the ingestion of *organic* ammonium salts is followed by an increase in the urea output. Recent experiments (Grafe and Schläpfer; Underhill and Goldschmidt; Abderhalden; Taylor and Ringer) indicate that there is some *retention of nitrogen* after the ingestion of ammonium salts. Underhill makes an exception of ammonium chloride and certain other of the *inorganic* salts of ammonium which he claims have a toxic action on the animal body. Water drinking with meals has been found to increase the excretion of ammonia, due to the indirect influence of an increased flow of a gastric juice of high acidity.

Under certain pathological conditions the output of urea may fall as low as 5 per cent of the total nitrogen of the urine. Such conditions are generally accompanied by a compensating increase in the ammonia

excretion. The output of ammonia may even constitute 40 per cent. or more of the total nitrogen excreted in the urine. In fevers and diabetes and other conditions accompanied by an abnormal acid formation, we find an increased ammonia output. In diabetes we find diacetic acid and oxybutyric acid in the urine combined with ammonia. This neutralization by the ammonia has prevented the withdrawal of fixed alkalis from the tissues for the neutralization.

It was formerly believed that the amino-acids resulting from protein digestion in the intestine were deaminized in the intestine and the liberated ammonia carried by the portal circulation to the liver and there constructed into urea. Recent experiments by Folin and Denis have demonstrated that there is no localization of the deamination process in the intestine and, furthermore, that the concentration of ammonia in the portal circulation is low and such ammonia as there is originates through the action of putrefactive bacteria in the *large* intestine.

Creatinin.—The older views regarding the significance of creatinin in the urine have experienced a marked change in recent times. The traditional opinion was that creatinin in the urine was largely derived from the creatin of meat ingested. More recent experiments have shown that creatinin and creatin are not lacking in the urine of suckling animals. That the creatinin output is at once increased by ingestion of meat has received abundant confirmation. On the other hand, both Long, and Chittenden and Mendel, have found creatinin abundant in the urine of vegetarians who abstained for months from meat or other creatin-containing foods. Folin maintains that the absolute quantity of creatinin eliminated in the urine on a meat-free diet is a constant quantity different for different individuals, but wholly independent of quantitative changes in the total amount of nitrogen eliminated. Creatinin in the urine would, on this assumption, become a measure of the extent of endogenous protein metabolism under appropriate conditions of diet. Whether creatinin production is increased with excessive muscular work is as yet rather uncertain, as is the immediate antecedent of the creatinin. Lecithin has been suggested by Koch as a possible precursor, though the evidence is far from convincing. That there is a production of both creatin and creatinin in starvation is well established. The excretion of creatinin is proportional, broadly speaking, to the body weight or bulk of the active tissues on diets practically creatin-free. We may have in creatinin a most reliable index as to the extent of certain aspects of protein metabolism—the tissue metabolism. Shaffer claims that creatinin results from some normal metabolic process which has its seat principally if not exclusively in the muscular tissue. The excretion of creatinin-nitrogen (mgs.) per kilogram of body weight he called the “creatinin coefficient.” Not much of value is known regarding the excretion of creatinin under pathological condition. Recently a pronounced increase in the creatinin excretion in nephritis has been reported by Erdélye.

Purins.—In the case of uric acid and other purin derivatives, there exists a twofold source, viz., an exogenous source related to the foodstuffs and an endogenous one. No convincing evidence has been furnished

of a synthetic formation of uric acid in man, although this is a familiar process in birds and reptiles where uric acid represents the chief end-product of nitrogenous metabolism. The exogenous sources of uric acid production are found in all those compounds which contain the purin nucleus in a form in which it can be attacked in the body. They include especially the nucleoproteins (nucleins) occurring abundantly in glandular tissues like liver, thymus, kidney, etc. To this may be added the free purin bases like hypoxanthin and xanthin which are present in tissue extracts, especially in the muscle. In smaller quantity, nucleic acid derivatives and purin compounds are found in vegetable foods. In all these cases, the purin group is either present preformed or is liberated by metabolic (enzymatic) changes and then oxidized further to uric acid, and in much smaller proportion appears in the form of other purin derivatives: xanthin, guanin, hypoxanthin, adenin, paraxanthin, heteroxanthin, etc. But even on a purin-free diet, or during starvation, uric acid continues to be eliminated in small, though noteworthy, amounts, and there is considerable evidence to show that this endogenous purin output is a fairly constant quantity for any individual, whatever the character of the (purin-free) diet. That the body is not entirely destitute of the power to form nucleoproteins is seen in the construction of these compounds in the developing egg and in the growing infant nourished with milk, which is practically purin-free. In the purin metabolism of the adult, food purins are of foremost importance and the synthetic processes, if they occur at all, are inconspicuous.

In attempting to render account of the intermediary metabolism of the purins, we have to deal with a chemical transformation which, as in the case of creatinin, is quite independent of urea production and calls for a special interpretation. For many years it was believed that uric acid represented an intermediate stage in the katabolism of proteins to urea. It is indeed true that uric acid can readily be decomposed so as to yield urea and such a process doubtless occurs when uric acid is broken down in the body. Further than this the relation does not hold, since we have learned to recognize chemical differences in the nitrogenous foodstuffs, involving the presence of the purin group in some, and an entire absence of it in others. As an illustration of this, we may cite experiments by Chittenden and Mendel, in which 20 grams of nitrogen ingested largely in the form of sweetbread (thymus glands rich in nucleoprotein) afforded an output of nearly 2.0 grams of uric acid, whereas the same quantity of nitrogen taken in the form of the purin-free substances yielded only 0.3 gram of uric acid per day. The quantity of uric acid (and other purins) eliminated is not equivalent to the amount ingested, but represents only a fraction of it. Simultaneously with the tissue processes which result in the oxidative formation of uric acid, a destruction of the latter occurs; so that the quantity of uric acid actually excreted represents the equilibrium reached between the formation and further oxidation of that compound. Recent studies make it probable that tissue enzymes coöperate in these changes in various ways. Nucleases may liberate the amino-purins, adenin and guanin, from nucleoproteins or nucleic acids; amidases (adenase and guanase) trans-

form these amino-purins to hypoxanthin and xanthin respectively; and oxidases effect an oxidation of the latter to uric acid and even further. All of these reactions have been demonstrated with various tissue extracts; and whereas many tissues, like the liver, testes, etc., which are rich in nucleoproteins, yield adenin and guanin on direct hydrolysis with acids, after autolysis they afford hypoxanthin and xanthin in place of the amino-purins. In addition to this, liver extracts are capable of oxidizing added xanthin and hypoxanthin to uric acid through intermediation of a special enzyme (xanthinoxidase), and to decompose the uric acid still further (Chittenden and Mendel). The liver doubtless plays an important rôle in these reactions, especially in the destruction of the intermediary uric acid. Herein probably lies the explanation of the increased (or at least undiminished) output of uric acid in organic disturbances of the liver, involving a complete or partial exclusion of its functions. Thus, too, we may believe that substances which disturb these functions, as alcohol, facilitate increased uric acid output by diminishing the normal katabolic action. At any rate, the organism has the capacity, invested no doubt in different tissues, of converting food purins into uric acid which may escape destruction and be excreted as such, or may be further oxidized. When the latter occurs, allantoin has been demonstrated as a characteristic product, rarely in man, however. It is not unlikely that oxalic acid represents a further intermediary stage.

The purin bases which serve as antecedents of endogenous uric acid have been supposed to arise from the nucleoproteins of disintegrated cells, in particular the leukocytes. As a matter of fact, increased elimination of uric acid has been observed in conditions attended with pronounced leukocyte destruction, enormous quantities (5 grams and over) having been reported in cases of leukemia. If we may trust the observations of Burian the greater bulk of the *endogenous* purins is formed in the muscles, explaining in a way the relative constancy of the endogenous uric acid production in the same individual as well as the variations attributable to different personality, *i. e.*, mass of active tissue.

Theories of Protein Metabolism.—Several general theories of protein metabolism have been advanced. The first of importance was that proposed by Liebig in 1842, who claimed that oxidation was not limited to the lungs but took place throughout the animal body in all active tissues and organs, and that the organic substances (fats and carbohydrates and that class of organic substances we now call proteins) were the substances oxidized. Liebig contended that of the three classes of foodstuffs, the proteins alone were utilized in tissue construction, and that the organized protein of muscular tissue, for example, was the source of the energy represented by muscular contraction or muscular work of any form. On the basis of this theory he denominated the proteins as tissue-building or "plastic" foods. Such foods he believed were subjected to a minimum amount of oxidation. The protein substances were decomposed solely under the influence of muscular work. On the other hand the fats and carbohydrates, the so-called "respiratory" foods of Liebig, readily underwent oxidation and in this way the heat of the animal organism originated. Liebig asserted that fats and carbo-

hydrates in contradistinction to the proteins were in no way interested in or related to the muscular activities of the organism. Their function was to undergo oxidation with the liberation of heat, and this oxidation could not be brought about through the influence of muscular work.

Voit's Theory.—Liebig's views were discussed and criticised by a large number of physiologists, the late Carl Voit, of Munich, being the most active of Liebig's critics. Voit contended at the outset that protein material might be katabolized under the influence of factors other than muscular work. He demonstrated that the ingestion of an excessive quantity of protein food by subjects maintaining uniform activity from day to day, was followed by an increased excretion of nitrogen. This could not occur provided Liebig's theory were true. According to this theory of Liebig the ingestion of an excessive quantity of protein material would be followed by the deposition or storage of this excess in the tissues. The excretion of nitrogen would remain uniform so long as the muscular activity remained uniform inasmuch as protein decomposition was brought about solely through this form of activity.

Finally out of this emerged Voit's theory, the so-called "luxus consumption" theory, first drafted in 1867. After undergoing material modification in accordance with experimental findings the theory of Voit was stated, in brief, as follows: The ingested protein is digested, absorbed, and transported by the blood stream to the various tissues of the organism or to their component cells. In these cells the protein material brought to them is katabolized *in solution*, in the cellular fluids, the nature and extent of the katabolism being determined by the living protoplasm of the cell. At no time, according to this theory, is there any katabolism of the living cellular protoplasm. As the cell substance is used up through the muscular activity of the organism it is replaced by the so-called "circulating protein" or "luxus protein" which has been brought by the blood from the digestive tract. In case an excessive quantity of protein is absorbed from the intestine it is oxidized in common with fats and carbohydrates as already mentioned, *without first becoming a part of the organized tissue*. There is, of course, a certain amount of living protoplasm which dies each day and this dead material after passing into solution would then be considered "circulating protein" and be subject to oxidation according to the same laws which govern the oxidation of the circulating protein derived from the ingested protein. We may consider that Voit conceived the living protoplasm of the cells to be in *suspension* as differentiating it from the circulatory protein which was in *solution*. He likewise asserted that the reason the cellular substance was not katabolized lay in the fact that protein katabolism took place *only in solution*.

Pflüger's Theory.—Pflüger was a severe critic of the theory of Voit. His ideas on protein metabolism were radically opposed to those of Voit and his Munich School. He, too, proposed a general theory of protein metabolism. According to Pflüger there is a very distinct difference between the circulating protein and the actual living protoplasm of the cell insofar as their *chemical structure* is concerned. The nitrogen of the living substance he believed existed in the form of *cyanogen*

radicals whereas the nitrogen of the dead protein was in the form of *amino* groups. Living protoplasm, he asserted, is extremely unstable and easily oxidized and this instability is due, in large part, to the "intramolecular movement of the atoms of the cyanogen radicals." The dead circulating protein, on the other hand, he maintained is much more stable and less easily oxidized. According to Pflüger before protein material can be katabolized it *must first be built up into the active living protoplasm or bioplasm of the cell*. It may then be subjected to the proper oxidative processes inseparably connected with protein katabolism.

When we consider all the evidence for and against the theories of Voit and Pflüger it appears that each theory has certain strong experimental evidence as a foundation. In the case of Voit's theory we have the observation that *a very large quantity of protein material may be katabolized in a few hours*. On the basis of Voit's "circulating protein" hypothesis such a finding is easily explainable. Pflüger's theory is rather inadequate in this connection. It would certainly be a startling conception to consider that the protein ingested in such excessive quantity has in the short interval elapsing been digested, absorbed, built up into living tissue substance and finally katabolized and passed into the blood stream where it was oxidized and from which its end-products were finally removed and eliminated by means of the kidney.

So far as Pflüger's theory is concerned the strongest evidence in its favor as against that of Voit, is the series of experiments reported by Schöndorff (1893). In these the blood from a fasting dog was perfused through the circulatory system of the liver and posterior limbs of a well-nourished dog and *an increase in the urea content of the blood was observed*. When the technique of the experiments was reversed, *i. e.*, when blood from well-nourished or fasting dogs was perfused through the circulatory system of the liver and posterior limbs of a fasting dog *no such increase occurred* in the urea content of the blood. These findings were quite generally accepted as indicating that circulating protein was not the efficient force in protein katabolism but that the factor of prime importance was the actively functioning animal cell. About twelve years after these experiments Folin in connection with a theory of protein metabolism to be considered, subjected the findings of Schöndorff to a most searching critical analysis. The protein katabolism of a fasting dog is of course greatly reduced. It is not surprising that there should be no appreciable increase in such katabolic processes when blood from well-nourished dogs was perfused in the manner indicated. In the case of the well-nourished dogs the conditions are different. These animals had been fed large quantities of meat (1000 to 1200 grams (per day and care was taken to kill them at the height of digestion. According to the theories of both Voit and Pflüger, therefore, it is logical to assume that the metabolic processes in the tissues of such animals were stimulated to a much higher degree than were the similar processes in the tissues of the fasting animals. Folin maintained that the simple fact that a certain amount of products of protein katabolism should be secured by the passage of blood through the tissues of such dogs is not surprising and cannot be offered as important evidence in favor of Pflüger's theory.

It is a question not of a simple increase in the urea content of the blood but is rather a question of *the extent of that increase*. Folin maintains that considering the sources of error and uncertainty which must be associated with an experiment such as Schöndorff performed, the extraction of 25 mgs. of urea-nitrogen from the posterior limbs of a dog killed while the animal in question was at the height of digesting 700 grams of meat cannot logically be accepted as proof that protein katabolism has taken place and that such katabolism occurred in the active cellular substance instead of in the circulating protein.

Notwithstanding the radical differences between the theories of Pflüger and of Voit there is one point of similarity which is of great importance. According to each theory protein katabolism is a *process of oxidation* and is brought about most activity in the muscular tissue. Each theory therefore presupposes the oxidation of fats, carbohydrates and proteins to take place in the muscles.

Folin's Theory.—A theory of protein metabolism which is much more generally accepted than those of Voit and Pflüger is that by Folin. According to this there are *two* different types of protein metabolism each of which is represented by the elimination of a distinct set of waste products in the urine. These types of metabolism are designated as the *exogenous* and *endogenous* respectively. The exogenous or intermediary metabolism is a *variable* form. It embraces the cleavage of the ingested protein molecules through a series of hydrolytic changes which have their inception in the intestine and which are ultimately completed in the cells of the various tissues. By means of these processes the protein-nitrogen is finally eliminated as urea. This form of metabolism, according to Folin, "yields chiefly urea and inorganic sulphates, no creatinin and probably no neutral sulphur." If the total katabolism be decreased the percentage excretion of urea and inorganic sulphates undergoes a simultaneous decrease. The second form of protein metabolism *i. e.*, the *endogenous* or *tissue* metabolism is a *constant* form, and embraces the *actual katabolism of the tissues of the animal body*. The course of the endogenous metabolism is represented by the urinary excretion of *creatinin* and *neutral sulphur* and in a less emphatic way by the output of uric acid and certain of the ethereal sulphates. The metabolic processes which yield these end-products may be taken to be of absolute necessity for the continuance of normal life processes. In other words, the end-products mentioned may be considered as an index of the activity of those processes which are inseparably connected with the living cell as distinguished from the non-living cell. A reduction in the total katabolism causes these end-products to become more prominent. Their actual output remains constant while their *percentage* output increases. Of all the end-products of this endogenous metabolism creatinin has come to possess the greatest significance.

According to the view of Folin the only nitrogen which is of absolute necessity to the animal organism is that which is derived from protein which is katabolized endogenously. If this is true then the major part of the protein *nitrogen* ingestion by the average individual under the customary dietary regime is not essential to the proper functioning of

the organism. If we accept this theory we must consider the active cleavage of the ingested protein as a process by which the nitrogenous portion is removed and excreted in order that the body may then utilize the non-nitrogenous residue. By this process the carbonaceous part, the so-called "carbon moiety" of the protein molecule, is rendered available. This may then be oxidized in a manner similar to the oxidations to which fats and carbohydrates are subjected. In this point Folin's theory is widely divergent from those of Voit and Pflüger. According to their theories the cells of the body always prefer to use protein for all purposes if proteins are available. From another standpoint the theory agrees with Voit as opposed to Pflüger. This is in the conception that living cellular substance is relatively *stable*. From still another viewpoint the endogenous metabolism of Folin is closely related to the metabolism of Pflüger's *bioplasm*. The conception that the greater quantity of the protein-nitrogen contained in the ordinary dietary is not needed by the organism has given a great stimulus to investigation. It is argued that special facilities have been developed by the organism through evolution processes, for the purpose of removing the nitrogen from protein substances in order that the "carbon moiety" of such protein might become available. We may consider that the primary step in this direction is the digestive hydrolytic cleavage into proteoses, peptones, peptides and amino-acids which occurs in the gastro-intestinal tract. These processes are supplemented by further transformations which have their seat in the cells of the various tissues. By means of these changes the unnecessary nitrogen is removed from the protein molecule. In this way a non-nitrogenous portion is obtained which has a relatively high fuel value, containing from 80 to 90 per cent. of the total energy of the protein. This carbonaceous residue may then be carried to the tissues and oxidized as needed, or it may instead be converted into carbohydrate or possibly fat. In the event of its transformation into fat or carbohydrate it would then ultimately be oxidized according to the katabolic regime which governs the cleavage of these substances.

Bearing the above facts in mind we can no longer take the urea output as an index of protein decomposition. Neither are we correct in calculating the energy liberation upon the basis of the urea output. This cannot be safely done inasmuch as the protein after yielding the portion necessary to the construction of urea, still maintains in the residual portion its original energy value but slightly lowered. It may be inferred from this that the non-nitrogenous foodstuffs may perhaps to advantage be substituted for a certain portion of the protein quota of the ordinary dietary. In fact this is one of the basic arguments underlying "low proteinism."

Let us review briefly some of the experimental facts upon the basis of which Folin formulated his theory of protein metabolism. He first placed six individuals upon a diet of 119 grams of protein, 148 grams of fat, and 225 grams of carbohydrate per day, thus roughly conforming to Voit's standard, and analyzed thirty twenty-four-hour urine samples collected from these six individuals. These analyses yielded data which according to our older views would constitute normal urinary data. He

next made certain feeding experiments, dividing each experiment into three periods. During the first period of three to four days the subject ingested the diet already mentioned. This may be considered as a "protein-rich" diet, containing as it does 119 grams of protein or 19 grams of nitrogen per day. After noting the characteristics of the urine eliminated upon this diet he substituted a "starch and cream diet" which contained approximately 1 gram of nitrogen as against the 19 gram ingestion of the previous diet. This low protein diet was continued for a week or ten days, after which a return was made to the protein-rich diet. A comparison was then made between the course of the nitrogenous and inorganic end-products of protein katabolism as they occurred in the urine during the feeding of the two distinctly different diets. By means of the most accurate methods available, Folin was able to secure what were doubtless the most accurate analytical data up to that time obtained from the analysis of urine. Many of the classic ideas as to urine composition were overthrown. For example, previous to this time it had been held that under all normal conditions the urea of the urine constituted nearly 90 per cent. of the total nitrogen of that excretion. By means of his starch and cream diet Folin was able to reduce the urea output to about 60 per cent. of the total nitrogen. An examination of his data showed that the output of inorganic sulphates was influenced in a like manner. On the other hand there were certain other urinary constituents which were excreted in practically uniform quantity from day to day no matter what the nature of the diet. Notable among these were *creatinin* and *neutral sulphur*. From a consideration of all the relationships brought out in his mass of data Folin evolved his view of protein metabolism which is probably the most acceptable theory yet proposed. Appended are the complete data from two urines of the same individual, one (I) collected during the "protein-rich" diet, the other (II) collected during the feeding of the "starch and cream" diet.

	I.		II.
Urine volume	1170 cc.		385 cc.
Total nitrogen	16.80 gm.		3.60 gm.
Urea-nitrogen	14.70 " = 87.5%		2.20 " = 61.7%
Ammonia-nitrogen . . .	0.49 " = 3.0%		0.42 " = 11.3%
Uric acid nitrogen . . .	0.18 " = 1.1%		0.09 " = 2.5%
Creatinin-nitrogen . . .	0.58 " = 3.6%		0.60 " = 17.2%
Undetermined nitrogen .	0.85 " = 4.9%		0.27 " = 7.5%
Total SO ₃	3.64 "		0.76 "
Inorganic SO ₃	3.27 " = 90.0%		0.46 " = 60.5%
Ethereal SO ₃	0.19 " = 5.2%		0.10 " = 13.2%
Neutral SO ₃	0.18 " = 4.8%		0.20 " = 26.3%

CARBOHYDRATE AND FAT METABOLISM

Carbohydrate Metabolism.—Carbohydrates apparently experience the best utilization of all the types of common foodstuffs. In the healthy infant, which receives these nutrients in the form of milk-sugar, no trace of sugar ordinarily escapes with the stools, and in the adult the record is scarcely less satisfactory for the digestible carbohydrates. They are, of course, not all absorbed in the form in which they are

ingested. Experimental evidence indicates that the monosaccharides (hexoses and pentoses) are the "physiological" sugars and that the digestible carbohydrates are converted into this form before they are absorbed and utilized. When soluble carbohydrates enter the circulation without intervention of the alimentary digestive processes they are only retained in part, depending on the nature of the compound introduced. The monosaccharides, dextrose and levulose in particular, are not excreted at once; but such carbohydrates as cane-sugar, milk-sugar, glycogen, or dextrans, reappear to a considerable extent in the urine when they enter the blood as such. The parenteral introduction of sucrose (cane sugar) has been studied by Mendel and Kleiner. When this sugar was introduced into dogs and cats in doses of 1 to 2 grams per kilogram body weight, 65 per cent. was excreted unchanged in the urine. According to Abderhalden, the 35 per cent. unaccounted for was hydrolyzed in the circulation through the activity of a *defensive* (protective) enzyme (sucrase) formed by certain cells upon the introduction of this foreign carbohydrate. Mendel and Kleiner failed to find sucrase in the blood of their animals.

Dextrose may be introduced into the circulation by a variety of channels and is in every case largely retained unless the quantity and rate of introduction are excessive. Under ordinary circumstances in man, the monosaccharide products of digestion are carried in the portal blood-stream to the liver, and doubtless go to form the glycogen store of this and other tissues.

Aside from glycogen, another important carbohydrate constituent of the body is the blood-sugar. This has repeatedly been identified as dextrose. Whether it exists there in the free state or in combination with other organic groups like the lecithins, or both, has not been answered to the satisfaction of all physiologists. Two facts deserve emphasis in considering the intermediary metabolism of the carbohydrates: namely, the relatively wide distribution and noteworthy quantities of glycogen which may be present in the body at one time, and the apparent constancy of the sugar-content of the blood. It seems to be demonstrated that there is no pronounced diminution of the percentage of sugar in the blood during starvation, although it is doubtless continually being requisitioned for the needs of the functioning tissues. Neither does work nor rest detectably affect the sugar-content of the circulation as a whole; and any condition in which hyper- or hypoglycemia arises partakes at once of the nature of disease. It is therefore apparent that some regulatory mechanism must be at work in the organism serving to maintain the constant level of the blood-sugar content.

How is this constancy maintained? How, on the one hand, is the surplus which the digestive processes furnish retained; and how, despite continued utilization, is the blood replenished with dextrose? Under ordinary circumstances of health, the blood contains about 1 per mille of dextrose. Whenever sugar tends to increase to any considerable extent beyond this and exceeds the limit of about 3 per mille, dextrose is eliminated by the kidneys. It is not unlikely that the intestine may act as an excretory organ at times when the sugar-content of the blood

becomes physiologically excessive and the kidneys are insufficient. These processes are normally not called into play; for the excess of carbohydrate is taken care of and retained in the organism or immediately burned up. But when this fails to be effected completely, an excretion of sugar may follow the intake of relatively large quantities of carbohydrate. The failure to retain or destroy the sugar intake may be a relative one and depend upon the quantity poured into the circulation at one time. When, however, the monosaccharide sugar is retained in the organism it is not always burned at once, but may be stored as glycogen.

There remains the second inquiry: How is the sugar-content of the blood maintained and the losses to the tissues made good? Without discussing this point we incline to the view that it arises from glycogen, notably in the liver. The blood-sugar rapidly sinks in quantity when the liver is cut out of the circulation; and it becomes difficult, if not impossible, to produce any typical hyperglycemia by experimental means, when the glycogen-content of the liver has previously been greatly reduced. In the conversion of glycogen into sugar, enzymes are doubtless concerned to an important extent. Soluble ferments capable of inducing such changes are known to exist, and there is no good ground for denying that the processes which can be observed postmortem in the liver go on during life, though perhaps at a greatly altered rate. A reaction of this type is, furthermore, quite in accord with prevailing views regarding the importance of enzymes for the chemical organization of living cells. And in attributing the vital process of sugar-formation to enzyme activity, it is unnecessary to postulate any extracellular secretion of the active agent; the modern view merely attempts to define more precisely the character of the chemical reaction involved by classifying it with those transformations known as enzymatic.

To be of use to the organism in furnishing energy, the carbohydrate must be burned. From the standpoint of energy transformations it makes little difference whether it is consumed rapidly and at once, or whether the decomposition goes on more slowly and in successive stages, as is the case in the living organism. To the physiologist, however, these *intermediary* processes are of no little concern; and for the physician they attain due significance in the light which appreciation of them throws upon many obscure pathological states. Experimentally, glycolysis, or sugar destruction, has been found to be characteristic of various tissues as well as of the blood. Undoubtedly, such destructive changes go on in the muscle during activity; but whether the glycolytic power of the muscular tissue is reinforced by contributions from other organs, such as an internal secretion of the pancreas, and whether the chemical reaction involved depends on the presence or absence of sufficient oxygen, cannot be said at present. Some investigators believe that the process of carbohydrate utilization in the body is comparable with typical fermentation changes as exhibited in the destruction of sugar by yeast or its zymase; for others the intermediation of oxygen in this internal respiration seems more important. Regarding the nature of

the products actually formed, little is definitely known at present; carbon dioxide is undoubtedly produced and various organic acids appear to arise in an intermediate stage. Perhaps we have in this the explanation of the tendency of an active tissue to become more acid when the circulation and oxygen supply are deficient. We regard it as extremely probable that the *paralactic acid* found in the animal organism has its origin in carbohydrates. Ordinarily it is further burned up; but when there is a lack of oxygen we have to deal with an incomplete combustion of the lactic acid derived by cleavage from sugar, without denying the *possibility* of a similar production from proteins.

In accordance with this view, a considerable excretion of lactic acid and sugar is found in poisoning with carbon monoxide, in which an oxygen deficiency is always manifested; and simultaneously with the formation of lactic acid a decrease in the glycogen reserve is noted. Another evidence of the inter-relationship between lactic acid and carbohydrate katabolism has been offered in cases of phosphorus poisoning. Here the urine contains paralactic acid; but when artificial diabetes is produced by means of phlorizin during phosphorus poisoning, the lactic acid disappears from the blood and urine with the appearance of the sugar produced by the phlorizin. Other clinical conditions in which paralactic acid appears in the urine are eclampsia and acute yellow atrophy of the liver. According to Mandel and Lusk, this indicates that "lactic acid produced from the cleavage and denitrogenization of protein, whether this occurs in the intestinal wall or in the liver or elsewhere, is first synthesized to dextrose within the organism (liver) before further distribution of the tissues. In the case of simple phosphorus poisoning this distribution of dextrose takes place with resultant anaërobic cleavage, leading to a second production of lactic acid." Following the old view of Hoppe-Seyler, the formation of lactic acid from carbohydrates and its elimination may be regarded as an abnormal process, occurring only under the conditions attending an insufficient supply of oxygen.

Another compound which doubtless owes its origin to the intermediary metabolism of the carbohydrates is glycuronic acid. This is obtained in the urine paired with camphor, thymol, menthol, and other compounds when the related antecedents are introduced into the body. Conjugated glycuronates are found in traces in the blood and liver; and the normal urine is said to contain very small quantities in combination with phenol, cresol, indoxyl, and skatoxyl. The possibility of a formation of glycuronic acid from proteins cannot be denied at present and the problem is associated with the broader question of sugar formation from proteins. But the available evidence points to carbohydrates as the chief, if not the only, source of this agent with which toxic compounds become conjugated and excreted in less harmful forms. Animals which have been starved sufficiently long to diminish to a minimum their carbohydrate reserve (glycogen) yield little, if any, glycuronate after ingestion of camphor. Reversely, the toxic action of some of the conjugated compounds can be greatly diminished by feeding carbohydrates which yield glycogen or dextrose in metabolism.

The glycuronic acid conjugation appears to take place in the liver, and the primary significance of its formation, therefore, probably lies in its detoxicating action. This is a well-known function of metabolic products of the proteins as we see it exemplified in the formation of ethereal sulphates (indican, etc.). In cases such as profound cocaine intoxication, when dyspnoëic conditions arise, glycuronates have been found in increased quantity in the urine. P. Mayer believes that, normally, the oxidation of dextrose in the body proceeds through the stage of glycuronic acid, and that when further katabolism is checked the imperfectly oxidized carbohydrate is eliminated in part in this form. Corresponding with this view, a simultaneous elimination of both glycuronates and sugar is observed under pathological conditions in which circulatory and respiratory disturbances play a part. A further step in the oxidative degradation of sugar is oxalic acid, which may likewise escape unburned under certain conditions.

Considering the preceding facts, it would appear as if carbohydrates may undergo fermentative decompositions in the body, or be decomposed through a succession of oxidative changes. Under conditions of imperfect oxidation one or more of these *intermediate* products may escape from the body. Glycosuria is thus only one evidence of a defective intermediary metabolism of the sugars. Glycuronic acid, saccharic acid, oxalic acid, lactic acid, and, perhaps, other organic acids primarily associated with diabetes are referable to the same source. Such a view may at any rate serve toward the construction of a tentative theory of intermediary carbohydrate metabolism.

Reference may be made to other less frequent anomalies of carbohydrate metabolism, such as pentosuria, levulosuria, lactosuria, and galactosuria. The excretion of lactose (milk-sugar), during and after pregnancy, is a temporary disturbance referable to an escape of the carbohydrates from the active mammary glands into the circulation. When these glands are extirpated, lactosuria is never observed. The excretion of levulose has been frequently reported and seems to occur in conjunction with dextrose elimination in many diabetics. The fact that dextrose can be converted in part into levulose in alkaline media makes this less difficult of interpretation. Galactose has been found in the urine of infants suffering with gastro-intestinal disorders. It represents an unutilized inversion product of milk-sugar absorbed from the intestine of milk-fed individuals. In explanation of the phenomena of pentosuria little can be said at present. The ordinary diet of man contains pentosans, which yield five-carbon sugars ($C_5H_{10}O_5$), such as xylose and arabinose, on hydrolysis. When pentoses are fed they are in part oxidized. It is unlikely, however, that the sugar eliminated in chronic pentosuria is derived from the food, since the elimination continues even during starvation. The nucleoproteins such as are found in the pancreas also yield pentose; but the latter is l-xylose, whereas the urine pentose appears to be arabinose. Ordinarily, there is no interference with the oxidation of the hexoses in pentosuria; and the condition may persist for years without exhibiting any other untoward symptoms. Pentosuria is of interest chiefly as an illustration of a curious and unexplained anomaly

of carbohydrate metabolism. Levene and Le Farge reported a case of pentosuria, the urine of which contained 0.25 per cent. of l-arbinose. Garrod groups pentosuria, albinism, cystinuria, and alkaptonuria together as *inborn errors of metabolism*.

Fat Metabolism.—In presenting a review of the present knowledge regarding the metabolism of fats, we shall be obliged to touch upon many topics still the subject of controversy, and the views expressed are not to be interpreted too rigidly. An adult man can digest 300 grams of fat per day, provided that it is offered in suitable form. What becomes of this after it leaves the alimentary tract? Furthermore we may inquire whether the tissue fat is derived directly from the ingesta or synthesized in indirect ways, and what are the chemical processes which inaugurate these transformations?

At the outset, the radical changes which prevalent ideas of fat digestion and absorption have experienced should be mentioned. A few years ago it was thought that fats were absorbed in the form of an emulsion, the undissolved and finely divided particles passing through the epithelial cells in some mysterious manner. This view has been altered for we have learned of the more extensive distribution of lipolytic enzymes in the alimentary tract, the process of fat cleavage apparently having a beginning in the stomach itself. Fatty acids and soluble soaps are formed in not inconsiderable quantities in the digestive tube. Furthermore, bile affords a medium for the solution of large quantities of free fatty acids at the temperature of the body. It is difficult to obtain indisputable evidence of the absorption of unchanged fat, except by histological methods perhaps not wholly reliable. Certainly other insoluble substances (such as fluid paraffin) are not absorbed even when they are finely emulsified, but are recovered *in toto* in the feces. While it is perhaps too soon to say that fats must be completely transformed by digestive change to soluble forms before they can be absorbed, it seems certain that such a preliminary cleavage or saponification does take place to a degree not formerly appreciated. Once beyond the lumen of the gut, the fragments are again synthesized to neutral fats. Foreign esters of the fatty acids reappear as glyceryl esters. There is some evidence that the lymphatic tissue-elements are concerned in these synthetic transformations.

When fats reach the blood-stream through the lymph channels, they are exposed to a peculiar metamorphosis which is still little understood. The suspended particles of the minute emulsion of the blood-fats may become changed into soluble and diffusible substances. Perhaps it is in this intermediary soluble form that fats are transported to the tissues, as we know carbohydrates to be. Regarding the nature of the processes a few definite statements may be ventured. The transformation is inaugurated by some constituent element of the erythrocytes which is destroyed by high temperatures; thus the change partakes of the nature of an enzyme reaction. It does not go on in the absence of oxygen, yet the chemical change certainly is not one of complete oxidation. The resultant product, unlike the original fat, is insoluble in ether and soluble in water. Neither is this fat metamorphosis a lipolytic change

of the usual digestive type, comparable with the cleavage produced by ordinary lipases. The latter appear to be almost completely wanting in the blood; the various body tissues are, on the other hand, supplied with more or less lipolytic power, so that we may postulate a widespread distribution of lipase in the animal body. The reversible action of fat-splitting enzymes, *i. e.*, the capacity of the same enzyme solution to synthesize neutral fats from fatty acids and alcohols, as well as to effect a corresponding cleavage of neutral fats, has directed attention to the probable important rôle of lipases in the tissue metabolism of fats. It is not unlikely, therefore, that the reserve supply of tissue fats is in some way transformed into more soluble forms by enzymes precisely as the storage glycogen may be, and thus transported from the tissue cells; while the deposition of transported fat components is perhaps accomplished by a synthesis in which enzymes are likewise effective agents.

Other esters are similarly attacked by tissue lipases. Enough has been said to indicate the actual occurrence of synthetic, lipolytic, and solvent enzymes for the fats. Connstein has offered the following tentative description of the immediate fate of food-fats. When ingested in the form of an emulsion, they may be in part hydrolyzed in the stomach; otherwise the lipolysis begins in the intestine. The cleavage products are absorbed and incidentally resynthesized to neutral fat, which reaches the blood through the chyle. In the circulation, the fat is transformed into a (at present unknown) soluble and diffusible modification which can readily pass through the capillaries, and thus gain direct access to the tissues themselves where a regeneration of fat goes on. When the fat depots in the tissues are drawn upon, lipolysis again takes place. Before accepting this it remains to be seen whether the emulsified particles of fat cannot pass through the walls of the capillary vessels in other than water soluble forms. The possible fat-dissolving power of the lipoids (lecithins, etc.) present in all cells is not to be overlooked in this connection.

The fat which enters the circulation is not unlikely in part involved very soon in the combustions continually going on. Where this katabolic change occurs can only be surmised; the liver is suggested, although the evidence is somewhat indirect. In greater part, the fat is undoubtedly first deposited, the most important depots being the subcutaneous connective tissue, the liver, and the folds of the peritoneum. The liver may become the seat of transitory or temporary storage. There exists in the liver a kind of antagonistic relation between glycogen and fat, as the result of which fat fails to accumulate in the liver so long as glycogen is abundantly formed there and the other fat depots are available. Thus it happens, as Rosenfeld has pointed out, that the livers of fattened pigs are frequently poor in fat, owing to their richness in glycogen; whereas fishes, which live on diets poor in carbohydrates (glycogen-formers), store up enormous quantities of fat in their hepatic cells. In man, with whom a mixed diet is customary, fatty liver is normally not observed for reasons just advanced. Lusk has pictured conditions when, owing to diabetes, or activity of the mammary gland in utilizing dextrose to form milk-

sugar, the cells affected become "sugar-hungry cells," which attract fat in greater quantity than they can burn it (fat infiltration).

The preceding remarks involve the assumption that tissue-fats may owe their origin directly to the food-fat, and lead to the broad question of fat-formation in the animal body. Such an assumption is more easily made in the case of fats because they are believed to undergo less radical changes in the process of digestion than do carbohydrates or proteins, and the resynthesis occurs in the passage through the absorbing cells. Kassawitz has modified the point of view somewhat by regarding the chyle-fat as a product of the internal secretion of the intestinal epithelial cells. From his standpoint the make-up of the circulating fat which is able to gain its way to the fat depots is dependent upon the protoplasmic activity of these living cells, a view which implies a somewhat indirect deposition of the fat ingested. Such distinctions are verbal rather than real. The important facts are, firstly, that when foreign fats possessing recognizable chemical and physical characteristics are fed, the constituent fatty-acid group which lends peculiar character to them can be detected in the tissue-fats. In the second place, despite variations in the character of the fat fed, there is an inherent tendency to maintain a typical constancy for the species and the particular depot under consideration. Mutton-fat differs from the fat of cattle even under somewhat similar conditions of diet; and in the same animal the fat has not the same composition in different parts of the body. These facts mean that various factors are at work in determining the make-up of the adipose tissue, and especially suggest other sources for body-fat besides the fat ingested. Among these, carbohydrates are without question the most important. The feeding of a diet rich in carbohydrate is a familiar method of fattening animals. It does not, however, afford rigorous proof of the origin of the fat produced, since every dietary of this sort usually contains an abundance of protein. In the formation of milk-fat we have a specific illustration of the relation of carbohydrates to fat formation. Jordan fed a cow during ninety-five days on a ration from which the fats had been nearly all extracted, and the animal continued to secrete milk similar to that produced when she was fed on the same kinds of grain and hay in their normal condition. The yield of milk-fat during the ninety-five days was 62.9 pounds. The food-fat eaten during this time was 11.6 pounds, of which only 5.7 were absorbed; consequently at least 52.7 pounds of the milk-fat must have had some source other than the food-fat.

The milk-fat in the above experiment could not have come from previously stored body-fat. This is supported by three considerations: (1) The cow's body could have contained scarcely more than 60 pounds of fat at the beginning of the experiment; (2) she gained 47 pounds in weight during this period of time with no increase of body nitrogen, and was judged to be a much fatter cow at the end; (3) the formation of this quantity of milk-fat from the body-fat would have caused a marked condition of emaciation, which, because of an increase in the body weight, would have required the improbable increase in the body of 104 pounds of water and intestinal contents. During fifty-nine consecu-

tive days, 38.8 pounds of milk-fat were secreted and the urine nitrogen was equivalent to 33.3 pounds of protein. According to any accepted method of interpretation, not over 17 pounds of fat could have been produced from this amount of assimilated protein. From these considerations, it is concluded that the milk-fat was produced in part at least from carbohydrates, as we know to be the case with body-fat.

The determination of the place where the conversion of carbohydrate to fat occurs is not easy. One is tempted to refer it to those places where carbohydrates accumulate, viz., the liver and muscles. But it is not less likely to be perfected in those locations where fat is deposited—in the cells of the subcutaneous adipose tissue, for example.

With reference to proteins as fat-forming elements, it is impossible to make any conclusive statement at present, notwithstanding the fact that there is strong evidence favoring such a view. The theory of fat-formation has been seriously modified in recent years. Even pathological fat-formation, typically described as "fatty degeneration" is now for the most part explained as a "fatty infiltration," *i. e.*, the introduction of fat transported from fat-depots to the "degenerated" tissue. Corresponding with this view, Rosenfeld and others have removed from "fatty" livers of dogs previously fed abundantly on some recognizable foreign fat and then poisoned with phosphorus, the characteristic foreign fat fed. The "degeneration" fat is in these cases not manufactured from the cell protoplasm, but transported and infiltrated.

In attempting to offer an explanation of the fatty metamorphosis in cells subject to toxic influences, we quote from Rosenfeld, the champion of the infiltration theory: When the protein content of the cell is attacked by any noxious agency, certain molecules of the protoplasm are thrown out of function. In order to maintain its vitality, the cell now obtains its energy in the oxidation of all the carbohydrates which it controls (hence the liver soon becomes glycogen-free) or when this is impossible the protein content is enriched by importation of protein. Accordingly it is observed that in many intoxications, as with phosphorus and alcohol, the protein content of the liver is increased. But when these various sparing agents are no longer available in sufficient quantity, the cell seeks the last help by attempting to recoup its losses with fat abstracted from the circulating blood which is in turn replenished from the fat-storage depots. With this infiltration of fat into the cell, the latter may succeed in maintaining itself and its energy transformation until the toxic effects have disappeared; if not, the infiltration is succeeded by a true degeneration and the cell dies.

Referring to the aspect of fat-metabolism afforded in the formation of milk-fat, the latter may, in the absence of an abundant fat-supply, be formed from carbohydrates. Under usual conditions, the fat of the milk is partly derived from the body-fat, but chiefly from the fat of the food. The fat is probably not transmitted directly from the blood, but is modified in the secreting cells of the mammary gland. If for any reason the quality of the milk is changed, there is always a tendency to return to the normal. The composition of the butter-fat is modified within narrow limits by the fat of the food; but the percentage of butter-

fat in milk is very little influenced by foods containing a large percentage of oil, or even by albuminous foods. Breeding rather than feeding seems to play the important part in determining the quantity and quality of milk; the fact that foreign fats do pass into the milk is, however, not to be overlooked and corresponds with the newer findings regarding the ready transportation of fat in the body from one depot to another. There is also some evidence in the case of the sebaceous glands tending to show an alteration in the make-up of their fatty secretion, depending upon the character of the fat fed. During embryonic growth, a consumption, rather than synthesis or deposition of fat occurs, insofar as can be judged from experiments on species which have an extra-uterine development. Thus a marked loss of fat is noted in the chick embryo during the process of development. The fresh egg containing 5.4 grams of fat may show a diminution to 2.7 grams or less.

Reference may be made to a group of compounds widely distributed in the body in all types of tissues and resembling fats in various ways. The lecithins, cholesterin and its esters, kephalins, and cerebrins, may be considered briefly under the general term of "lipoids" or "lipins." These are fat-like compounds, which differ widely among themselves, but possess the general physical properties and solubilities of fats. They are especially prominent in the nervous tissues, and their behavior toward the volatile anesthetics is made the basis of the Meyer-Overton theory of narcosis. Of the metabolism of these substances, little can be said. Lecithins disappear from the cells far less readily than do the ordinary fats; their content is far more constant so that they appear to be an integral part of the protoplasm. In the disintegration of nervous structures, decomposition products of lecithin (cholin, glycerylphosphoric acid) appear to be liberated, as well as in certain autolytic changes.

Of the stages through which fats pass in their katabolism to the end products, water and carbon dioxide, very little has been ascertained. As in the metabolism of carbohydrates, pathology has shed some light. In severe diabetes, when carbohydrates are not burned up, fats are drawn upon. In this condition, as also in inanition, the "acetone bodies" may be eliminated in considerable quantity. Formerly, these compounds were attributed to the proteins; but at present, they are generally associated with metabolism of the fats, and presumably represent products of the incomplete oxidation of higher fatty acids. In health, and on the customary mixed diets, only a few milligrams of acetone are excreted daily. In hunger, the quantity may increase to over a gram per day. Carbohydrates (and perhaps alcohol) check this production at once, but not proteins or fats.

Corpulence is scarcely to be regarded as a pathological manifestation of fat metabolism. Direct observations have failed to indicate any diminished capacity of the organism to burn the deposited fats. We have rather to deal with a disproportionate relation between intake of food and food utilization. Whatever apparent diminution in energy transformation may occur is attributable primarily to the relative muscular inactivity of corpulent individuals. A small daily excess may lead to a considerable accumulation of body-fat.

METABOLISM DURING FASTING

We may recognize *three* types of fasting: *first*, fasting in which there is abstinence from *both food and water*, the respired oxygen being the only contribution brought to the organism from without; *second*, fasting in which there is abstinence from food, but water is allowed *ad libitum*; *third*, fasting in which there is abstinence from food, but the fasting subject is fed a *uniform volume of water* daily. The first does not differ very materially from the second, inasmuch as a fasting organism drinks comparatively little water, the daily ingestion decreasing progressively until there is finally *total abstinence*. The third type differs materially from the other two, inasmuch as a uniform volume of water is daily ingested notwithstanding the fact that the body weight of the fasting subject is decreasing. In other words, the water ingestion per unit of body weight increases progressively from the beginning to the end of the fast. The longest fasts on record are those of the third type. For the physician and pathologist the subject of fasting possesses additional practical interest, in view of the fact that the essential derangements in many cases of under-nourishment are qualitatively comparable with those noted during complete starvation, the differences being of degree only.

Some of the characteristic features of metabolism in hunger are illustrated in the study of protein metabolism. The output of nitrogenous katabolic products tends to diminish after the earlier days of starvation, ultimately reaching a fairly constant level. This would seem to indicate that protein katabolism is stimulated during the first two or three days; and the increased output of nitrogenous products during this period seems to vary somewhat in proportion to the richness of the previous diet in protein. It is certainly unlikely that the high values for urinary nitrogen found in the earlier period of starvation are due to a liberation of retained excretory products which are suddenly swept out of the system under the altered nutritive conditions. In seeking to explain this repeatedly observed increase in protein katabolism, Voit was led to make his well-known distinction between "circulating" and "morphotic" or "tissue" protein in the body. The morphotic protein is disintegrated only to a small extent in the ordinary course of metabolism; that is, it represents the relatively stable nitrogenous component of the cells. The more readily metabolized circulating protein, the supply of which is largely dependent on preceding conditions of nutrition, is used up during the early days of inanition. In this way the early high nitrogen output is explained by the Voit school. The succeeding fall in nitrogen excretion represents a stage in which other tissue components are destroyed in place of the residual and more stable morphotic protein. Fat and glycogen now afford a part of the energy required. This explanation has not received universal acceptance. In the few experiments on man, this temporary increase in the rate of nitrogen katabolism has not always been as marked as in the experiments on animals. Among other explanations of the phenomenon a few deserve mention, especially because

they illustrate what a wide range of complicating factors may influence the behavior of the body in metabolism. Thus the "nutritive plane" of the individual has been called upon to account for the relatively high or low nitrogen output in the early period of starvation. When the intake of nitrogenous food is suddenly cut off in young individuals accustomed to a high protein metabolism, the cells do not at once adapt themselves to the new conditions, and the high rate of protein katabolism is continued until new relations are gradually established. Again, a larger or smaller intake of water in starvation is effective in increasing the output of nitrogenous compounds, in fasting as well as when food is given. Finally, most of the prolonged starvation experiments on man have been undertaken with individuals in whom the reserve store of non-nitrogenous nutrients was relatively low. This, too, may help to account for the high output of nitrogen.

In brief periods of starvation some observers, notably Prausnitz, have regularly found a higher output of nitrogen on the second day than on the first. This is referred to the rapid consumption of glycogen during the early period of hunger, with a consequent protection of the protein from decomposition. In animals a prolonged period in which the extent of nitrogen katabolism is fairly low and constant indicates a uniform progress of the decompositions in the body—a feature to which other facts likewise point. Finally, a period is reached in which the disintegration of body protein rapidly increases, indicated by a twofold or threefold increase in the nitrogenous compounds eliminated. This "premortal" rise in nitrogenous output is the sign of impending death. By most investigators it has been referred to the exhaustion of the glycogen and fat depots of the body. When the latter are no longer available, the protein resources become severely taxed and the tissues rapidly disintegrate to furnish the energy requisite for the bodily functions. Death is thus attributable to the lack of available nutrients in the tissues. The sudden premortal rise in nitrogen elimination has been ascribed by others to a sudden widespread disintegration of body cells due to the improper nutritive conditions to which they are finally subjected. The amount of materials available in the starving body before death intervenes may be very great—in animals as much as 70 per cent. of the original store of energy.

During starvation, heat production remains remarkably constant, and the body temperature is maintained until near the end, or the period when profound metabolic changes give evidence of themselves in the sudden and rapid increase in nitrogen output. So far as has been experimentally observed the oxidative processes maintained during hunger do not decrease in extent below the values noted in the same individual under comparable conditions when food is not denied. This is apparently true not only in periods of rest, but likewise during work. The actual extent of protein katabolism during fasting is indicated by the data in the table on page 608. These were taken from experiments by Munk, Van Hoogenhuyze and Verploegh, and Howe, Mattill and Hawk. It has been established that injected or ingested amino-acids are utilized as usual by the tissues of a fasting individual.

	Cetti, 57 kilos.			Breithaupt, 60 kilos.			Flora Tosca.			"E."		"H."	
	Nitrogen output in urine. Grams.	Protein equivalent. Grams.		Nitrogen output in urine. Grams.	Protein equivalent. Grams.		Nitrogen output in urine. Grams.	Protein equivalent. Grams.		Nitrogen output in urine. Grams.	Protein equivalent. Grams.	Nitrogen output in urine. Grams.	Protein equivalent. Grams.
Before fasting . . .	13.49	84.9		13.02	82.0		13.99	87.5		10.43	65.2	9.81	62.3
First fasting day . . .	13.54	85.3		10.01	63.1		8.76	54.7		10.07	62.9	8.34	52.1
Second fasting day . . .	12.58	79.3		9.92	62.5		8.38	52.3		15.07	94.2	11.10	69.4
Third fasting day . . .	13.21	82.7		13.29	83.7		10.73	67.1		14.46	86.4	12.82	80.1
Fourth fasting day . . .	12.39	78.1		12.78	80.5		9.40	58.7		13.08	81.8	12.12	75.8
Fifth fasting day . . .	10.69	67.4		10.95	68.9		7.87	49.2		11.80	73.8	11.18	69.9
Sixth fasting day . . .	10.10	63.6		9.98	62.2		7.73	48.3		11.21	70.1	10.41	65.1
Seventh fasting day . . .	10.85	68.6			6.11	38.2		10.73	67.1	10.16	63.5
Eighth fasting day . . .	8.90	56.1			7.70	48.0					
Ninth fasting day . . .	10.83	68.2			7.35	45.9					
Tenth fasting day . . .	9.46	59.7			6.80	42.4					
Eleventh fasting day		6.14	38.4					
Twelfth fasting day		6.97	43.5					
Thirteenth fasting day		5.62	35.0					
Fourteenth hunger day		4.08	25.4					
First day of feeding . . .	13.35	84.1		11.88	74.2		7.23	45.2		11.40	71.3	11.00	68.8

The metabolism of the elements other than nitrogen during prolonged starvation has not been extensively studied in man except in a few instances. The output of sulphur appears to run closely parallel to that of nitrogen, indicating a common source of the two elements in the disintegration of protein. The elimination of phosphorus has been found to be increased both absolutely and relatively with respect to nitrogen. If the phosphorus excreted in starvation is likewise derived from proteins it should obviously bear the same relation to the nitrogen excreted as the two bear to each other in the body. This has not usually been the case. In addition to the high output of phosphorus, an increased elimination of calcium and magnesium, too great to be attributed to the disintegration of muscle tissue, has also been found. These facts, taken together, leave little doubt, that the bones, which are so rich in phosphates of the alkali earths, suffer loss.

Since the chlorides of the urine are primarily derived from the chlorides (chiefly NaCl) taken with the food, a rapid fall in the output of chlorides during starvation is naturally to be expected, and has repeatedly been observed. The excretion of potassium considerably exceeds that of sodium, quite the reverse of ordinary conditions. This adds another to the many evidences, during starvation, of the disintegration of the tissue elements (structures) in which potassium salts greatly preponderate.

So far as experiments indicate, the formation of the feces does not cease during prolonged starvation, although the quantities are greatly diminished. The composition of the "hunger feces," viz., the relatively high content of nitrogen (6 to 8 per cent.), fat, and inorganic salts, recalls the feces discharged after an easily digestible diet, free from cellulose. This close resemblance has contributed largely to the prevailing view that the feces are not to be considered as the undigested residue from food to any great extent under satisfactory conditions of diet, but rather as consisting in large part of bacteria and secretory products from the alimentary tract.

We cannot attempt to follow the fate of the many other katabolic products arising during hunger, nor designate the specific changes produced in individual organs. One is impressed, however, by the slight extent of the variations from the normal. The differences between fasting and normal individuals are quantitative rather than qualitative, at least during the earlier stages of starvation. The chemical make-up of the tissues which remain unused in a starving animal is not noticeably altered. The proportions of nitrogenous decomposition products obtainable are entirely comparable with those yielded by a well-fed animal of the same species. The creatin content of muscle, however, has been shown to undergo considerable variation, there being a possible slight increase in the first part of the fast followed by a very pronounced decrease in the final stages of the fast.

The fat content of the blood may be found notably higher during the early days of starvation. This corresponds with what might be expected if fat is transported during hunger from its storehouses in the body to the places where the oxidations take place. The blood of a fasting subject will show increased values for hemoglobin, erythrocytes, and

leukocytes, provided no water is ingested. In case water is permitted the above values will be subnormal. The changes in the distribution of the various forms of leukocytes during prolonged fasting have received but little attention. Tauzk reports a decrease in the relative number of mononuclear lymphocytes and an increase in the eosinophile and polymorphonuclear leukocytes during a thirty-day fast of Succi; Benedict showed an increase in polymorphonuclear leukocytes, a decrease in small lymphocytes and an increase in large lymphocytes as a result of fasting. In general the eosinophile count was low and the mast-cell count high. Howe and Hawk report the data from two fasting men as indicating "an increase in the percentage of the polymorphonuclear leukocytes at the beginning of the fast, followed by a decrease below normal at the end of seven days; the opposite conditions held for the lymphocytes. There was an increase in the percentage of large lymphocytes during the earlier part of each fast."

Closely related to the conditions pertaining in complete inanition or "acute" starvation, are those found in the more chronic forms of *deficient* nutrition ("Unterernährung") or malnutrition. Unfortunately we have few accurate experimental data on this subject. The cases in which deficient nutrition may arise are numerous, and in all we have to deal with physiological conditions not markedly different from those discussed under complete hunger. It is possible that the organism adapts itself to the deficiency in intake by a more economical utilization of its resources, so that the body can maintain its nutritive equilibrium with a smaller expenditure of energy. Accurate data are not yet available in this direction, while evidence to the contrary is not wanting. Von Noorden believes that even after prolonged deficient nutrition an intake of 30 large calories per kilo of body-weight is required to maintain equilibrium. Practical experience, however, has shown that under poor nutritive conditions, persons may make gains on diets which are barely sufficient for the well-nourished individual. A careful study of this subject is important; for in conditions (such as gastric ulcer) in which larger quantities of food cannot be consumed without danger, a knowledge of body needs becomes invaluable.

Loss of Weight during Fasting.—In starvation, the body is living on its own tissues—that is, katabolizing body constituents to liberate the energy requisite for the necessary bodily functions. As might be expected, the character of metabolism in inanition depends in no small degree upon the previous nutritive condition.

A question which presents itself is this: How great are the losses which the body can sustain during hunger without serious impairment of function? The losses in body weight ascertained in the most carefully conducted researches on starving men are collected in the table which follows (Weber and others):

Subject and Observer.	Duration of fast. Days.	Body weight.		Percentage of loss of body weight.	
		At beginning. Kilograms.	At end. Kilograms.	Total.	Per day.
Cetti (Senator et al.)	10	57.00	50.60	11.2	1.1
Breithaupt (Senator et al.)	6	60.00	56.40	6.0	1.0
Succi (Luciani)	30	63.20	51.80	19.0	0.6
Swede (Johannsen)	5	67.80	62.80	7.4	1.5
S. A. B. (Benedict)	7	59.52	55.84	6.2	0.9
Beauté (Cathcart)	7 ¹	65.61	60.23	8.2	1.2
"E" (Howe, Mattill and Hawk)	7	74.20	68.70	7.4	1.0
"H" (Howe, Mattill and Hawk)	7	70.30	64.90	7.7	1.1
"E" (Howe and Hawk), repeated fast	7	76.60	71.40	6.8	0.9

The adipose tissue suffers the earliest and greatest diminution. Among the residual (fat-free) organs, the glands will be noted to undergo a proportionately large loss, others—especially skin, central nervous system, and heart—experiencing less change. It has been pointed out that the tissues suffering the relatively smaller losses include those whose function is of greatest importance for the continuance of life.

Glycogen disappears from the body with varying readiness in starvation. The loss of protein is extremely variable and in animals starved until death the diminution of their protein-content ranged, in E. Voit's experiments, between 22 and 49 per cent. These variations are attributable to the different fat reserves of the animals. Those which experienced the smaller losses (22 to 26 per cent.) showed a considerable supply of fat even after death. They suffered from protein starvation; that is, certain essential organs must have experienced a loss of protein greater than they could withstand. Presumably, these must have been specific *essential* organs, since most of the tissues can withstand a far greater loss—even 50 per cent.—than is here indicated. In those animals where a larger loss (49 per cent.) of protein was noted, the fat had been reduced to a minimum; and the animals must have satisfied the demands for energy during the later days of starvation almost entirely with protein. Here, then, we have both fat and protein starvation.

The bones of normal and fasting animals of the same species give no evidence of any marked change in percentage composition. The bone substance is decreased in quantity as the result of a fast, but its composition is apparently unchanged.

Length of the Fast.—The length of time the human body may function without food is largely a question of individuality. There are numerous fasts recorded ranging in length from two to fourteen days. Of the longer fasts the most authentic are the thirty-day fasts in which the professional faster Succi served as subject. Very recently Benedict has carried out a thirty-day fast on a professional faster which will no doubt prove to be the most comprehensive and important fasting investigation yet made.

Influence of High-water Ingestion during Fasting.—There is considerable evidence in favor of the belief that an increased water ingestion stimulates protein katabolism in fasting as well as in normally nourished organisms. One of the first tests of the influence of water upon the

¹ First part of fast.

fasting animal was made by Forster. He fasted a dog seven days and upon the eighth day increased the water ingestion of the animal 1828 cc. Under this augmented water intake the output of urea was increased from 12.14 grams for the seventh day to 22.91 grams for the eighth day. The total volume of water fed the dog upon the eighth day was 3000 cc., the entire volume of the fluid being fed within a half-hour interval. Heilner worked with a fasting dog and showed that an increase of 2000 cc. in the water ingestion produced increases in the urinary nitrogen from 3.15 grams to 4.09 and 3.58 grams respectively. One of the most comprehensive experiments along this line was recently reported from the writer's laboratory (Howe, Mattill and Hawk). In this test the fasting dog "Oscar" was fed 700 cc. of water by a tube, during each day of a fifty-nine-day fast. On each of the next four days the water ingestion was increased to 2100 cc. The accompanying table shows the distribution of urinary nitrogen during the course of this experiment:

INFLUENCE OF HIGH-WATER INTAKE DURING FASTING¹

Day of fast.	Body weight.	Volume of urine.	Specific gravity.	Reaction of urine.	Total N.	Urea N.	Ammonia N.	Creatinin N.	Creatin N.	Purin N.	Allantoin N.	Undetermined N.
Fasting—700 cc. Water per Day												
54-	Kg. 16.34-	Cc. 449	1006	acid	Gm. 2.986	Gm. 2.555	Gm. .278	Gm. .172	Gm.	Gm. .015	Gm. .011	Gm.
57	15.98											
58-	15.90-											
59	15.78]											
Fasting—2100 cc. Water per Day												
60	16.09	1385	1002	acid	5.097	4.054	.469	.223	.034	.005	.036	.276
60	15.79	2390	1002	acid	3.690	2.980	.362	.174	.071	.004	.024	.075
62	15.89	1685	1001	acid	3.096	2.430	.391	.142	.032	.002	.036	.063
63	15.32	1840	1002	acid	2.793	2.203	.284	.138	.045	.002	.028	.093
Fasting—700 cc. Water per Day.												
64	14.94	820	1004	acid	2.256	1.796	.224	.118	.032	.002	.016	.038
65	14.71	640	1004	acid	3.016	2.421	.268	.159	.022	.012	.018	.113
66	14.64	545	1005	acid	2.173	1.790	.192	.107	.021	.007	.010	.046

The increased excretion of total nitrogen during the high-water period when taken into consideration with the increased output of total purin nitrogen (purin + allantoin) and the appearance of creatin in the urine are believed to furnish strong substantiation for the hypothesis that the increased nitrogen output associated with increased water ingestion is due to a true stimulation of protein katabolism rather than to a flushing of the tissues. The pronounced increase in the ammonia excretion during the period of increased water ingestion is interpreted

¹ From the *Journal of Biological Chemistry*, 1911, x, 417.

as indicating that the large volume of water had caused a pronounced stimulation of the gastric function (Wills and Hawk).

Intestinal Putrefaction during Fasting.—The course of the processes of intestinal putrefaction in the fasting organism has been but very little studied. One of the earliest investigations of prime importance was made by Fr. Müller in connection with one of Cetti's fasts. At the time these tests were made the output of total ethereal sulphate was considered to be the index of the extent of putrefaction within the intestine. However, in the investigation under consideration Müller determined the output of urinary indican as well as the total ethereal sulphate output. It is surprising that Cetti's urine was said to be free from indican after the third day of fasting. Upon the ingestion of food subsequent to the fast, indican was again present. Inasmuch as juices and secretions containing protein material are poured into the intestine even during periods of inanition it is surprising that no traces of indican were detected in the urine subsequent to the third fasting day. In this particular fast the last stool from the feeding period was not passed until the seventh day of the fast, which would tend to the absorption of increased quantities of indol and augmentation of the indican output.

According to Weber the excretion of total ethereal sulphate continues during fasting but is notably decreased as has been shown in experiments on both Cetti and Succi. Baumstark and Mohr have offered evidence from fasting studies in favor of the theory that indican may be considered an index of intestinal putrefaction. They concluded that putrefactive processes continue in the intestine of fasting animals so long as the "fasting feces" are retained in the intestine. After the excretion of such feces, however, the urine contained no indican. (In the experience of the writer, "fasting feces" continue to be excreted throughout a fasting interval of over one hundred days.) Baumstark and Mohr argue that their observations furnish verification for the general belief, established by Folin and others, that indol formed in the intestine is the sole source of the indican content of the urine and that it does not arise from the cleavage of tissue protein during fasting.

Certain experiments from the writer's laboratory (Sherwin and Hawk) have shown a pronounced decrease in intestinal putrefaction, as measured by the urinary indican output, during a seven-day fast of a 76 kilogram man. The output of urinary indican for the second day of the fast was 60.5 mg., whereas that for the seventh day was 13.7 mg.

"This pronounced decrease in the amount of indican excreted during the fast was, of course, the natural outcome of the non-ingestion of food. Inasmuch as the putrefaction processes and the consequent formation of indol in the lumen of the intestine are dependent entirely upon the passage of protein material into the intestine it was to be expected that the withdrawal of food from the subject would result in a marked lowering of the indican values of the fasting urines. Various juices and secretions, however, continue to be poured into the intestine during fasting and the protein constituents of the unabsorbed portion of these fluids would form a medium for the development and activity of the varied types of intestinal bacteria, among them the indol-formers. For this reason

even after prolonged *initial* fasts it is probable that there is ordinarily not a complete cessation of intestinal putrefaction. This would be particularly true in case the fasting subject drank rather large volumes of water each day of the fasting interval, as did the subject of this fast. It has been demonstrated quite conclusively that water ingested in large amount causes an increased outpouring of both the gastric and pancreatic secretions" (Sherwin and Hawk).

Certain unpublished data (Sherwin and Hawk) regarding the putrefaction processes during the course of the one hundred and seventeen and one hundred and four day fasts of the dog "Oscar" are of interest. The urinary indican data for the entire second fast and a part of the first fast are herewith tabulated:

117-day fast.		104-day fast.	
Day of fast.	Indican output per day. mg.	Day of fast.	Indican output per day. mg.
1 to 4	26.6	1 to 4	17.6
30 to 33	18.7	5 to 8	10.3
80 to 82	19.1	26 to 29	10.4
92 to 95	12.9	42 to 45	9.5
104 to 107	14.6	54 to 57	4.9
115	19.2	66 to 690
116	17.5	78 to 810
117	27.3	90 to 930
		102 to 1050

The data indicate that there was a pronounced intestinal putrefaction up to the very end of the *first* fast of one hundred and seventeen days. During the *repeated fast* of one hundred and four days, which began several months after the close of the first fast, the conditions surrounding the putrefactive processes in the intestine were profoundly altered. In this repeated fast the output of indican was *much lower than in the first fast*. Moreover, there was a gradual decrease in the putrefactive processes from the first to the fifty-seventh day of the fast and from this point until the fast ended upon the one hundred and fifth day *there was no further sign of intestinal putrefaction* as indicated by the urinary indican output. The data apparently warrant the conclusion that the prolonged initial fast (one hundred and seventeen days) had in some way enabled this animal to more satisfactorily control the putrefaction processes within his intestine when he was again subjected to a similarly prolonged fast. Whether this lowered putrefaction was due to the lessened activity of the indol-forming organisms or to some other cause is not apparent. There is no basis for believing that the protein secretions of the intestine were not present in as copious quantity during the second as during the first fast.

Creatin and Creatinin in Fasting.—The excretion of creatinin, which under conditions of normal feeding exhibits marked uniformity from day to day (Folin, Schaffer and others) does not exhibit this regularity of excretion in the case of the fasting organism. In fasting a gradually *decreasing* output of creatinin is observed. Under normal conditions creatin does not appear in the urine. Its appearance in the urine of the adult is believed to have a pathological significance. Fasting is one of the conditions in which there is an elimination of creatin in the

urine. The creatin excreted during fasting is believed to have its origin in muscle. In a study made by Howe and Hawk the creatin content of the muscle of the fasting animal showed a marked decrease (over 60 per cent.) while the nitrogen content of similar muscle was but slightly lowered. This pronounced decrease of creatin in fasting muscle accompanied by a nitrogen value but slightly below normal was considered sufficient grounds for assuming that the total amount of excreted creatin did not necessarily represent the creatin obtained from completely and permanently disintegrated muscular tissue. They drew the conclusion that the creatin was derived either from disintegrating muscular tissue or was removed in some manner from such tissues which were still functioning within the body. Dorner has also reported a decrease in the creatin content of rabbit muscle as a result of fasting, whereas Biddle and Howe have made similar findings in the case of dog muscle.

Noël Paton believes that "if the muscle 'flesh' katabolized as calculated from the creatin excreted be greater than the total 'flesh' disintegrated as calculated from the total nitrogen eliminated, the conclusion may be drawn that there has been a retention of some of the muscle protein nitrogen, due either to resynthesis in the muscle or to transference to some more essential organ. On the other hand, when the 'flesh' katabolized, calculated from the output of total nitrogen, exceeds that calculated from the output of creatin, the stored nitrogen, *i. e.*, the circulating or surplus protein of Voit, has been broken down." This theory of Paton's is very plausible and attractive and is of material aid in the explanation of many metabolic phenomena.

Cathcart has said, "As creatin is only present in considerable amount in muscle tissue, and as muscle tissue is much reduced during the course of starvation, it must be concluded that it is the liberated creatin which is excreted and that the creatin-free nitrogenous rest is utilized for the building up of tissues more immediately essential to the animal."

Mendel and Rose in experiments upon rabbits and hens found an *increase* in the creatin content of fasting muscle. They interpret this as indicating an *increased formation* of creatin in the muscle during fasting. Myers and Fine have reported rather conclusive evidence on the question of the relation of fasting to the creatin content of muscle. They find that "The elimination of creatin in the urine increases with the length of the fast and in the days preceding death relatively large amounts are eliminated. This results in a depletion of the creatin supply of the body and in a *decreased* content of muscle creatin." The above authors find that "The creatin content of rabbit muscle is relatively increased in the *early part of starvation*."

Curves in a chart from repeated fasts showed that as the fasts progressed the curve representing the creatinin excretion descended, whereas that representing the creatin excretion ascended, and the two curves crossed a few days before the fall in the nitrogen output which precedes the "premortal rise." In every fasting experiment made in the writer's laboratory when the test has been carried to the premortal rise in nitrogen excretion the crossing of the creatin and creatinin curves has been observed. Moreover, this "creatin crossing" occurs with great

regularity at practically the same point with reference to the premortal rise. The "creatin crossing" appears to have considerable significance and to furnish a possible means of estimating the probable length of the antemortem period. It is a fact worthy of note that in the case of the one hundred and seventeen-day fast mentioned elsewhere the creatin and creatinin curves *did not cross* and no difficulty was experienced in bringing the animal back to his normal condition by careful feeding.

Repeated Fasting.—Several repeated fasts have been reported, the greater number being upon lower animals. In repeated fasts on pigeons and roosters, Seeland showed that those birds which were subjected to repeated fasts of one to three days' duration gained weight more rapidly, their tissues were more solid, and the birds hardier and stronger than the control birds which were fed every day. In a repeated fast (Howe and Hawk) a fox terrier was brought into nitrogen equilibrium and then subjected to two fasts. On the fifteenth day of the first fast the premortal rise in nitrogen output was noted and was accompanied by other signs indicating that death would result in a few hours. She was then carefully fed and during a feeding period of forty-seven days regained her former weight and was again brought into nitrogen equilibrium, after which she fasted a second time for thirty days. The animal was in fully as good physical condition at the commencement of the second as she was at the commencement of the first fast. The water ingestion was uniform throughout the feeding and fasting periods. The loss in body weight was much slower in the second fast than in the first. This is shown by the fact that the animal lost 45.75 per cent. of her body weight during the first fast, whereas on the fifteenth day of the second fast, *i. e.*, after a period equalling in length the entire first fast the loss in body weight was but 25.42 per cent. During the first fast the tissue disintegration (as measured by the urinary nitrogen output) was *high and rapidly increasing*, whereas during the second fast it was *low and fairly constant*.

As a result of tests on repeated fasting it seems fair to conclude that in repeated fasting there is a slower and less profound tissue disintegration during the second fast. This may be interpreted as indicating *a greater resistance acquired as the result of the initial fast*. This increased resistance noted in such experiments following fasting may indicate that the "repeated fast" if properly regulated may possess important therapeutic properties. The observation (unpublished) of Dietrich that after fasting the animal utilized its food more satisfactorily than before is of interest in this connection (Howe). The fasting procedure had so reduced the plane of metabolism that the quantity of food which was insufficient for maintenance before fasting was afterward sufficient not only for maintenance, but to produce a positive nitrogen balance as well. Fasting had increased the metabolic efficiency of the animal.

The extent to which nitrogen may be retained by a fasting organism during the period of feeding subsequent to the fast is shown in the table on page 617, which includes data secured in an experiment made upon two fasting men in the writer's laboratory (Howe, Mattill and Hawk). One of the surprising features is the excessive quantity of food eaten

by these fasting men during the period of feeding subsequent to the fast. Subject E ingested 50 per cent. more nitrogen (21.107 grams) upon the *second day* after the fast than he was normally accustomed to ingest (14.043 grams) as shown by the data for the preliminary period, whereas subject H upon the *first day* after the fast ingested nearly 25 per cent. more nitrogen than he ordinarily ingested under conditions of normal feeding. Through the medium of this high protein diet E regained 90 per cent. of his lost weight in *four days*, whereas H approximately (99.6 per cent.) *regained his original body weight in five days*. No discomfort was experienced by the subjects following the ingestion of the excessive diet so soon after the close of the fast.

NITROGEN RETENTION AFTER FASTING

		Subject "E."					Subject "H."		
Day of period.		Nitrogen in food. Grams.	Nitrogen in urine and feces. Grams.	Nitrogen balance. Grams.	Day of period.		Nitrogen in food. Grams.	Nitrogen in urine and feces. Grams.	Nitrogen balance. Grams.
PRELIMINARY PERIOD (FOUR DAYS)									
Average	14.043	12.396	+ 1.480		Average	12.138	11.806	+ 0.332	
FASTING PERIOD (SEVEN DAYS)									
1	10.182	—10.182	1	8.483	— 8.483		
2	15.182	—15.182	2	11.242	—11.242		
3	14.573	—14.573	3	12.966	—12.966		
4	13.190	—13.190	4	12.261	—12.261		
5	11.911	—11.911	5	11.321	—11.321		
6	11.320	—11.320	6	10.552	—10.552		
7	10.840	—10.840	7	10.303	—10.303		
FINAL FEEDING PERIOD (EIGHT DAYS)									
1	13.465	14.697	— 1.231	1	14.988	13.265	+ 1.723		
2	21.107	12.534	+ 8.573	2	18.800	13.188	+ 5.612		
3	19.817	13.512	+ 6.305	3	14.100	11.956	+ 2.144		
4	18.820	13.648	+ 4.828	4	14.100	11.934	+ 2.166		
5	18.800	14.801	+ 3.999	5	18.800	11.513	+ 7.287		
6	17.740	14.120	+ 3.620	6	12.793	10.871	+ 1.922		
7	15.242	14.800	+ 0.442	7	12.138	11.468	+ 0.690		
8	14.043	15.387	— 1.344	8	12.138	12.373	— 0.235		

INFLUENCE OF WORK ON METABOLISM

Among the influences which affect metabolism, muscle-work is perhaps of even greater significance than the food intake. The effects are immediate and the extent of the change produced is far greater than the measure of the work done would seemingly indicate; for the most part, the skeletal (voluntary) muscles outrank the non-striated (involuntary) ones in the extent to which they participate in these effects. When a

muscle contracts, heat is liberated, and work is done. The relative distribution of the energy between these two effects varies somewhat with the conditions under which the contraction is carried out. Within certain limits, as Fick demonstrated, the working capacity increases with the demand made upon the muscle.

The law of the conservation of energy teaches that the various manifestations of energy, such as heat, work, etc., can be expressed in common terms; and the relation between heat and mechanical work is shown in the equation, 1 large calorie = 425 kilogrammeters. On this basis, the potential energy of the foodstuffs can be expressed in terms of the maximum work which they can afford approximately as follows:

1 gram of protein yields	1700 kilogrammeters
1 gram of fat yields	4000 kilogrammeters
1 gram of carbohydrate yields	1700 kilogrammeters

Actually, however, much larger quantities of the foodstuffs must be katabolized to yield mechanical work in this amount; roughly, about one-fifth to one-quarter of the total energy is thus convertible. The extent to which metabolism may be increased by work under normal conditions is best illustrated by actual figures. In experiments covering forty-nine days on healthy adults, the average total energy given off per day during rest, with food, was 2262 large calories; during work in the same individuals, over sixty-six days, the daily average was 4676 large calories. Of this twofold increase (2400 calories), 450 calories were equivalent to the extra muscular work done.

The influence of muscular work on metabolism is speedily evident by an increased consumption of oxygen and output of carbon dioxide. The respiratory quotient is normally less than 1. Not all of the oxygen reappears again in the eliminated carbon dioxide, since some of it is used in the oxidation of other elements to form water, sulphuric acid, and other bodies. In the combustion of pure carbon, one volume of oxygen yields one volume of carbon dioxide. In the body the magnitude of the respiratory quotient depends on the nature of the katabolized substances. For the combustion of carbohydrates it is approximately 1; in the katabolism of proteins it is about $\frac{8}{10}$; and for fats the ratio falls to $\frac{7}{10}$. The respiratory quotient will accordingly vary in accordance with the relations here expressed, and may afford important information regarding the nature of the katabolic processes. Experience has shown that the consumption of oxygen by the tissues is independent, within wide limits, of the oxygen supply, but varies directly with the demand of the tissues. In view of this, the extent of oxygen consumption may be taken as a measure of the action of different influences on the rate of metabolism. Studies have been made on the effects of walking, marching, swimming, mountain climbing, etc., upon respiratory metabolism. Zuntz and Katzenstein have estimated the intensity of the metabolic changes which work brings about in man. Expressed in the consumption of oxygen per minute, in contrast with the conditions prevailing during rest, they found: During rest 263 cc., walking on level 763 cc., walking up hill 1253 cc.

Higley and Bowen made a study of the immediate changes in the excretion of carbon dioxide incidental to muscular work in bicycling. The results agree with those of previous workers in indicating a uniform output of carbon dioxide during uniform work. The changes which give rise to this katabolic product in the muscle may be pictured as beginning instantly with the commencement of the work. Since the gas must first diffuse into the blood and then be carried to the lungs, there should be a latent period of a little more than half the time required for a complete circuit of the blood before the first waste product formed during work can be exhaled. A variation of several seconds may reasonably be expected, dependent upon the rapidity of the circulation. The latent period of increase in the output of carbon dioxide from the lung in case of beginning work is nearly twenty seconds, the increase reaching its maximum in about two minutes. Upon cessation of work, the output decreases again to the normal amount in about the time occupied by its increase and after a like latent period.

In view of the rapid adjustment of the carbon dioxide output to the muscular metabolism occurring, it might be expected that the extra elimination during work would be confined almost entirely to the daytime when the work is done. This is actually the case; and during the night periods it is only a little larger in the work experiments than in the rest experiments.

The proportions of carbon dioxide, water, and heat, eliminated during the different periods of the day in the same individual at rest and at work, with and without food, are shown on page 620 (Atwater and Benedict).

It is well known that a given amount of mechanical work is not always done at the same cost of materials metabolized. Training and fatigue are important factors in considering the expenditure which a given muscular task calls for. In general, the trained and untired muscle is the more economical; that is, it transforms less material in doing a given amount of work than does the untrained or fatigued muscle. Other circumstances, among which are atmospheric conditions (oppressive heat, humidity, etc.), the relative strain on specific muscular parts, the absolute amount of work to be done, as well as personal factors—all influence the capacity for work and the relative expenditure of energy. The increased expenditure of energy which is called forth by exertions which ordinarily pass unnoticed may be not inconsiderable. The mere maintaining of the body in an upright position calls for a consumption of 10 to 20 per cent. more oxygen than is used in quiet repose. The varied activity of the hands and arms makes corresponding demands on the energy supply. In sleep we have the extreme contrast to muscular activity in work; and although the consumption of oxygen and the output of carbon dioxide, for example, fall to about three-fourths of the figure quoted in the waking state, it is scarcely less than what can be attained by complete relaxation during waking hours. In general, there is an increase of about 40 to 45 per cent. in carbon dioxide output during waking rest over absolute relaxation; a figure which illustrates the physiological significance of repose in therapeutics.

We have reserved any discussion of the influence of muscular work upon nitrogenous metabolism for this place, because it bears directly upon the question of the source of the energy transformed in this condition of bodily activity. Is work done at the expense of proteins, fats, carbohydrates, or two or more of these body constituents? With respect to the proteins, the problem admits of a ready experimental answer. If an individual is maintained in nitrogenous equilibrium upon an *adequate mixed diet*, the effect of muscular activity ought to manifest itself in a distortion of the nitrogen balance if proteins are katabolized to supply energy for work. It seems obvious that if an individual is fed over long periods on a ration largely or exclusively composed of proteins, the source of muscular work must be found in increased protein katabolism. Similarly when the supply of non-nitrogenous food is inadequate to furnish all the energy needed, the conclusion is inevitable that nitrogenous compounds will be disintegrated to supply the demands. It has been observed that animals fed over long periods of time on lean meat alone are capable of performing severe muscular labor. Although the nitrogenous excretion has been observed to be increased under such conditions, the protein katabolized was too small to account for the energy expended in the work; such experiments, however, give no sufficient reason for concluding that the body performs work *preferably* at the expense of protein material. What do observations made under other conditions of diet teach?

The classic experiment of Fick and Wislicenus (1866) was, perhaps, the first satisfactory attempt to compare the energy expended during work with that rendered available by the protein disintegrated. They calculated that the quantity of proteins katabolized during an ascent of the Swiss Faulhorn (6500 feet), and measured by the urea excreted, was insufficient to account for more than a small fraction of the energy required to raise their bodies to the height of the mountain, not to mention the energy expended in the work of the internal organs and muscular movements not directly involved in the ascent.

Contrary to these results, various investigators have found more or less increase in protein metabolism after muscular work. In those instances, it has usually been found that the diet selected was insufficient for the demands made upon the body. Where the food supply has been in excess of the amount required for maintenance, any material increase in the nitrogen excretion as the result of the work done has usually been overlooked.

The increase in the excretion of nitrogenous waste during extreme activity may reasonably be attributed to a decomposition of tissue protoplasm, incited perhaps by fatigue or deficient respiration in individual groups of muscles, as Speck has maintained. In many experiments made in this country, under the auspices of the Department of Agriculture, no similar influence has been found; and no evidence whatever has been obtained to indicate that proteins are the sole source of energy in muscular work. Armsby has summarized the evidence now available:

"1. The non-nitrogenous ingredients of the food or of the tissues are the chief source of muscular energy. In by far the greater number,

if not all, of the experiments upon this subject the amount of protein metabolized, as measured by the nitrogen excretion, was insufficient to furnish energy equivalent to the work done, the deficiency being in many cases very great. This statement, it will be observed, does not assert that the proteins are not concerned in the production of this energy. We may regard it as very probable that the non-nitrogenous matter metabolized has first entered into the structure of the muscular protoplasm, which, as we know, consists largely of proteins; but in a contraction it is largely, if not wholly, the non-nitrogenous group contained in the protoplasm which are metabolized rather than the nitrogenous groups.

"2. With insufficient food there may be a considerable increase in the protein metabolism, as a result of muscular exertion, especially when pushed to exhaustion.

"3. This increase is far from sufficient to supply energy for the work actually done, is not proportional to it, and seems dependent to a considerable degree upon accompanying conditions.

"4. With sufficient food the increase of the total protein metabolism consequent upon the muscular exertion is at the most slight and possibly equal to zero.

"5. In some cases a storage of proteins has been observed to result from the performance of work."

It would be a mistake to conclude that the proteins of the body play no part in the work of its muscles. The muscle protoplasm is built up of both nitrogenous and non-nitrogenous components; and while the readjustments which take place during the contractile processes involve a destruction of the non-nitrogenous constituents, perhaps in the form of sugar or glycogen, both components appear to be requisite for the proper maintenance of an active working apparatus. It is thus quite conceivable that with an inappropriate protein supply muscular power might be impaired seriously, even though the liberation of energy in the actual contractile changes goes on at the expense of the carbohydrate groups of the protoplasm. We may picture the latter as a labile substance when the easily detached non-nitrogenous groups are joined to it. Muscular activity would accordingly involve a change in the stability of the protoplasm, which in turn would resume its original condition of irritability by becoming regenerated through the addition of fresh carbohydrate groups. Several experimental observations are more easily interpreted from this point of view. For example, it becomes evident that protein alone will not accomplish the regeneration of the contractile substance in a satisfactory degree, although in its disintegration it may furnish a considerable proportion of non-nitrogenous groups—the so-called "carbon moiety" of the protein molecule. Again, if the proteins form a semi-passive agent, as it were, in the development of muscular power, it is plain why the muscles may be more capable of retaining protein when they are active, than is the case with inactive or less vigorously working muscles. Herein lies the explanation of the phenomena of muscular hypertrophy; and experiments have indicated a greater tendency for the body to gain protein during light work and

abundant diet, than is observed in a less active condition. We have here indicated the distinction between "putting on flesh" (growth of muscle) and storing up foodstuffs. We must distinguish between the *development* of a well-organized muscular system calling for a liberal protein supply, and the maintenance and *working* demands of such organs—*i. e.*, between the construction of the machine and its energy requirement. Finally, the participation of the body proteins may apparently be provoked by unfavorable conditions for muscular work, to some of which reference has already been made and among which oxygen starvation is a conspicuous example. Thus, in the muscular exertion of dyspnoea the increased protein decomposition seems to be attributable to local conditions in the muscles involved. The katabolic processes in these organs are qualitatively altered and fatigue products are more speedily formed.

At present, it is practically impossible to ascertain with certainty what choice, if any, the body exercises between fats and carbohydrates in the decomposition of non-nitrogenous compounds in muscular work; nor can we say that the fats are transformed into sugar or glycogen before they become available for the immediate work of the contractile tissues. The more recent studies upon isolated muscles, especially the heart, are very suggestive. These show that such organs can maintain active contractions for many hours, when they are supplied by perfusion with an oxygen-laden isotonic solution of inorganic salts and dextrose. Blood serum or protein solutions are not more effective than solutions of common salt—all of which are decidedly inferior in sustaining power to Ringer's solution with sugar. It would seem from this that the sugar solution is effective not so much in washing away fatigue products—the muscle waste—as in supplying a nutrient group. Otherwise, we should expect equally effective results from simple saline perfusion. Within the body as a whole, it is not so easy to analyze the function of the individual non-nitrogenous nutrients in muscular work. We have seen that the respiratory quotient varies for the different kinds of materials consumed in the body. A review of the literature suggests that when the body is well supplied with carbohydrates the respiratory quotient remains high during work, indicating a large utilization of carbohydrates. The latter are thus readily used when they are available for the cells of the body; and accordingly the store of glycogen in the muscles is seen to diminish with severe work. On the other hand, metabolism experiments on man fail to indicate any difference in the way the body utilizes the kinetic energy arising from oxidation of the different nutrients. Atwater and Benedict have tested the relative efficiency of fats and carbohydrates by ascertaining whether it costs more energy to do the same work with fats than with isodynamic amounts of carbohydrates. In directly comparable work experiments a somewhat higher efficiency for the carbohydrate than for the fat-diet was observed.

In other experiments not so comparable, less pronounced differences appeared. The general conclusion of the investigators is "that in these experiments the fats were slightly inferior to isodynamic amounts of carbohydrates as a part of a ration for muscular work. But while the

natural inference is that calorie for calorie the carbohydrates were slightly superior to the fats as sources of muscular energy, the difference observed was very small and may have been due to some individual peculiarity of the subject with which the more directly comparable experiments were made, rather than to any inherent capacity of the materials to yield energy for external muscular work." Regarding the immediate sources of muscular energy and the character of the substances actually metabolized in the muscles, these experiments give no answer; nor is the solution apparent in the lack of more extensive information respecting the intermediary changes in metabolism.

FOOD REQUIREMENTS AND STANDARDS

The question of the food requirements of people is a very important one. Practically from the time investigators were able to differentiate, in a rough way, between fats, carbohydrates and proteins those workers who were interested in nutrition problems have been suggesting the varying amounts of these dietary constituents which should be daily ingested by individuals in the various walks of life. The methods employed in this line of investigation were, at the outset, of necessity rather crude. These have, however, been developed and elaborated and today are far more accurate and efficient than ever before. There are two principal ways by which we may obtain data to form a basis for our deductions as to the real food requirements of the human organism. These are, first the so-called *dietary studies*, and second the more accurate type of *metabolism experiment*. Dietary studies are generally made on groups of individuals of a certain class, the study extending over a considerable period of time. The plan of these studies, in general, is first to determine, as closely as possible the quantities of various foods and food mixtures these individuals consume per day. Then occasionally through the actual analysis of samples of each of these foods or food mixtures, but more often through application of factors derived from previous analyses of dietary constituents of a similar character, the quantity of fat, carbohydrate and protein ingested per individual per day is determined. These values are then expressed in grams and termed "food standards," "standard diets," or "standard food requirements." It is unnecessary to say that food standards based upon data secured from this type of investigation are not as dependable data as are those secured from the application of the accurate, modern metabolism procedure.

In setting a food standard for any particular individual it is essential to plan such standard in accordance with the body weight and vocation of the individual in question. It needs no argument to convince us that an average 100 kg. man requires a larger food ration than does an average 50 kg. man. In like manner also it is logical to assume that a day laborer should consume more food than a bank clerk of the same body weight. The variation in the food requirements does not effect the protein requirement so much as the energy requirement. In the course of the prolonged and pronounced muscular effort of the laborer,

a much larger amount of fat and carbohydrate is burned than in the body of the sedentary individual. In order that the body remain normal and functionate efficiently it is necessary that the hard-working individual shall ingest a diet which has a much higher fuel value than has the diet of the person engaged in sedentary pursuits. Inasmuch as protein metabolism is not influenced to any marked degree by muscular work it is not essential that the protein portion of the diet of the hard-working individual shall be increased above that of the sedentary person to such an extent as are the fat and carbohydrate quotes.

Data compiled from a large number of dietary studies by Langworthy and Milner (U. S. Department of Agriculture) are reproduced in the table on page 626. Regarding such data, Chittenden and Mendel say "data such as the foregoing compilation afford, merely disclose the dietetic *habits* of these individuals. It is unfortunate that more facts derived from actual studies of metabolism are not yet available, so that wide-reaching applications cannot be made, based upon *physiological* conditions, for it has become somewhat questionable whether the current statistical standards represent the true needs of the organism. Custom and convenience have entered so largely into our modes of living and dictated so much in our alimentary habits, that we may be in danger of accepting their dictum as a physiological law without that critical revision which scientific consistency demands." If the standard diets are examined it will be noted that Chittenden suggests a diet which contains about 50 per cent. less protein than any of the standards suggested up to that time. The following discussion of this standard is quoted from Chittenden and Mendel:

"How far are we justified in assuming the necessity for the rich protein diet called for by the Voit standard and those like it? It is repeatedly stated that an abundance of food is a necessity for the maintenance of physical vigor and muscular activity. This view is certainly reinforced by the customs and habits of mankind; but we may well query whether our dietetic habits will bear criticism, and in the light of modern scientific inquiry we may even express doubt as to whether a rich protein diet adds anything to our muscular energy or bodily strength.

"The experiments hitherto reported have been continued only for brief periods; and recalling the marked resistance of the healthy body it would be amiss to draw any far-reaching conclusions from observations of this character. Further, attention must be given to the unfavorable effects which have been attributed to a low protein diet fed to dogs for some time. Thus, Munk and Rosenheim both noted, after six to eight weeks, a loss of the power of absorption from the alimentary tract, loss of body weight, strength, and vigor, followed by death. One is impressed, in the study of these animal experiments, with the abnormal if not unhygienic conditions under which the dogs were kept. The great monotony in the diet and restricted quarters to which they were subjected makes it highly questionable whether the diet of the animals was responsible for their poor health in the sense in which it has usually been interpreted. In prolonged experiments over seven hundred days on man, Neumann has found 70 to 80 grams of protein per day to suffice for the maintenance

SUMMARIZED RESULTS OF DIETARY STUDIES IN THE UNITED STATES (QUANTITIES PER MAN PER DAY.)

	Number of studies included in averages.	ACTUALLY EATEN.				DIGESTIBLE.				Fuel Value.
		Protein.		Fat.	Carbohydrates.	Protein.		Fat.	Carbohydrates.	
		Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	
PERSONS WITH ACTIVE WORK.										
Rowing clubs in New England.....	7	155	177	440	143	168	427	3415	3955	
Bicyclists in New York.....	3	186	186	651	171	177	631	3535	5005	
Football teams in Connecticut and California.....	2	226	334	634	208	336	615	3790	5390	
PERSONS WITH ORDINARY WORK.										
Farmers' families.....	10	97	130	467	89	124	453	3415	3955	
Mechanics' families.....	14	103	150	402	95	143	390	3535	5005	
Laborers' families in large cities.....	12	101	116	344	93	110	334	2810	3840	
Laborers' families in more comfortable circumstances.....	2	120	147	534	110	140	518	3925	5390	
PROFESSIONAL MEN.										
Lawyers, teachers, etc.....	14	104	125	423	96	119	410	3220	3580	
College clubs.....	15	107	148	459	98	141	445	3580	5390	
MEN WITH LITTLE OR NO EXERCISE.										
Men in respiration calorimeter.....	11	112	80	305	103	76	296	2380	2845	
PERSONS IN DESTITUTE CIRCUMSTANCES.										
Poor families in New York City.....	11	93	95	407	86	90	395	2845	3200	
Laborers' families in Pittsburg, Pa.....	2	80	95	308	74	90	299	2400	2845	
MISCELLANEOUS.										
Negro families in Alabama.....	20	62	132	436	57	125	423	3165	3625	
Negro families in Virginia.....	19	109	159	444	100	151	342	3625	4085	
Italian families in Chicago.....	4	103	111	391	95	105	379	2965	3200	
French Canadians in Chicago.....	5	118	158	345	109	150	335	3200	3625	
Bohemian families in Chicago.....	8	115	101	360	106	96	349	2800	3200	
Inhabitants of Java Village, Columbian Exposition, 1893.....	1	66	119	254	61	18	246	1450	1810	
Russian Jews in Chicago.....	10	137	103	418	126	98	405	3135	3625	
Mexican families in New Mexico.....	4	94	71	289	86	67	595	3460	3940	
Chinese dentists in California.....	1	115	113	389	106	107	281	2620	3080	
Chinese laundrymen in California.....	1	135	76	566	124	72	549	3480	3980	
Chinese farm laborers in California.....	1	144	95	640	132	90	621	3680	4140	
Fruitarians.....	6	50	102	237	43	92	225	2055	2400	
Maine lumbermen.....	182	337	512	812	312	512	812	6995	7955	

ration, even with moderate additional food intake of 90 grams of fat and 300 grams of carbohydrate. He inclines to the belief that nitrogenous equilibrium can be maintained on various nutritive planes. Vegetarians have lived for years on a diet relatively poor in proteins without observing any disagreeable effects. Jaffa's observations on the fruitarians and nutarians of California "showed in every case that although the diet had a low protein and energy value, the subjects were apparently in excellent health and had been so during the five to eight years they have been living in this manner." In comparing the income and outgo of nitrogen on a diet composed mainly of nuts and fruits, it was observed in 2 subjects that 8 grams of nitrogen were sufficient to bring about nitrogen equilibrium, while with 2 other subjects the nitrogen required daily for equilibrium was about 10 grams. In harmony with Sivén, Jaffa believes that after the body has suffered a loss of nitrogen there is at once an effort to attain nitrogenous equilibrium, and that any gain of nitrogenous body material is a comparatively slow process. If this is true, it is obvious that the living substance of the tissue protoplasm must be *slowly* formed from the protein of the diet. This, says Jaffa, should serve as a warning to anyone contemplating any appreciable decrease in the protein of the daily diet.

"A further statement made by Jaffa serves to illustrate the attitude taken by many physiologists on this question. "Even if it could be proved," he writes, "by a large number of experiments that nitrogen equilibrium can be maintained on a small amount of protein, it would still be a great question whether or not it would be wise to do so. There must certainly be a constant effort on the part of the human organism to attain this condition, and with a low protein supply it might be forced to do so under conditions of strain. In such a case the bad results might be slow in manifesting themselves, but might also be serious and lasting. It has also been suggested that when living at a fairly high protein level the body is more resistant to disease and other strains than when the protein level is low." While these suggestions merit careful consideration, it is equally evident that there is another side to the question. The elimination of the excess of nitrogen may become physiologically burdensome and uneconomical, if not positively harmful. Hence, we may well query on which side lies the greater danger without magnifying it on the one hand or suppressing efforts directed toward the true protein minimum on the other.

"With the purpose of throwing light upon the question of the protein minimum and ascertaining how far, if at all, the intake of protein food can be diminished without deleterious effects, an extensive series of experiments on man has been conducted in the laboratory of the writers. Recognizing that the maintenance of nitrogen and body equilibrium on a lower protein standard than that generally adopted would have little practical value and would not escape justifiable criticism unless the period of trial was extended over a long time, arrangements were made to realize this as far as possible. The experiments were conducted upon three distinct types of individuals: (1) Professional men who while leading active lives were not engaged in very active muscular work.

They represent the mental rather than the physical worker. (2) A detail of men from the Hospital Corps of the United States Army, as representatives of the moderate worker. These men, of different ages and temperaments, took vigorous systematic exercise in addition to the routine work connected with their daily life as members of the hospital corps. (3) A group of university students who were thoroughly trained athletes, and some of them with exceptional records in athletic events. The records of these observations have already been published in Chittenden's *Physiological Economy in Nutrition* from which the data here presented are taken.

"The method of observation consisted in a daily collection and measurement of urine and feces. The nitrogen output in the urine was accurately determined throughout the experiment, extending from six to nine months or longer. At intervals the daily loss of nitrogen in the feces was determined. Finally the balance between income and outgo of nitrogen was exactly ascertained several times for periods of about a week. The total intake of food in terms of heat units was approximately estimated without direct measurement. The statistics on this point are therefore of subordinate value. It may be noted that the body weight of some of the individuals gradually fell until a certain stationary "level" was reached, about which small daily fluctuations were observed. This was true of all who had any considerable accumulation of reserve fat. In the well-trained men of slender or athletic build these initiatory changes in weight were not so apparent, if they occurred at all. One of the writers (C), of 57 kilos body weight, showed an average daily nitrogen output of 5.7 grams in the urine for nearly nine consecutive months. Nitrogen equilibrium and body weight were maintained. The other writer (M), with a body weight of 70 kilos, established from an original weight of 76 kilos, likewise maintained health, strength, and equilibrium with an average daily output of 6.5 grams of nitrogen in the urine. A third subject (U), of 65 kilos body weight, maintained health without increasing the total fuel value of the food, with an average daily output of about 7.5 grams of nitrogen for many months. These figures imply a daily protein metabolism equivalent to about 0.1 gram of nitrogen per kilo of body weight, or half of that which custom and habit prescribe.

"It should be said that these limits could only be reached with maintenance of nitrogen equilibrium, provided the total food supply was adequate. Our estimates indicate that the latter, far from being excessive, tended to fall below the ordinarily accepted standard of 3000 large calories for a man of average body weight and moderate work. The adaptation to the new standards was gradual in each case.

"The results obtained with the soldiers, living on a prescribed diet and exposed to the strain of military duties, together with gymnastic work and training confirm the conclusions arrived at with the professional group from which some data are quoted above. Once accustomed to a more sparing protein diet, less rich in nitrogen, these subjects had no difficulty in maintaining body weight on the food provided, and when the conditions were satisfactorily adjusted nitrogen equilibrium could

readily be preserved. The members of the soldier detail were able to live for five consecutive months with a protein metabolism corresponding to about 8 grams of nitrogen per day without discomfort or loss of vigor. The athletes, as well as the physically less active men, likewise met their ordinary requirements for several months on an average daily protein intake of about 60 grams. Moreover, careful tests, made at regular intervals on the soldiers and athletes, indicated an increase in muscular strength while the men were on the restricted diet. The summary given below of a balance experiment lasting one week will illustrate the general character of the nitrogen results obtained in all of the experiments. The subject was a vigorous athlete of 63 kilos body weight.

NITROGEN BALANCE

	Nitrogen taken in. Grams.	Nitrogen in urine. Grams.	Weight of feces (dry). Grams.
May 18 . . .	8.119	5.75	
May 19 . . .	9.482	6.64	15
May 20 . . .	10.560	8.45	
May 21 . . .	8.992	8.64	
May 22 . . .	9.025	8.53	
May 23 . . .	8.393	7.69	89
May 24 . . .	7.284	7.34	24
			128—contain 6.40% nitrogen
	61.855	53.04	+ 8.192 grams nitrogen
	61.855 grams nitrogen		61.232 grams nitrogen
	Nitrogen balance for seven days	=	+0.623 gram
	Nitrogen balance per day	=	+0.089 gram
	Average nitrogen intake per day	=	8.830 grams

"It is interesting to compare the previous dietetic habits of some of our subjects in respect to the protein intake. During two weeks, at the beginning of the experiment on the soldiers when the ordinary army ration was used, the daily output of urinary nitrogen not infrequently exceeded 20 grams and usually reached over 16 grams (equivalent to 100 to 125 grams of protein). The subsequent record of these subjects is given below:

Name.	Body weight. October, 1903. Kilos.	Body weight. April, 1904. Kilos.	Average daily urinary nitrogen, November-April. Kilos.	Metabolized nitrogen per kilo of body weight. ¹ Kilos.
Fritz . . .	76.0	72.6	7.84	0.106
Oakman . . .	66.7	62.1	7.42	0.116
Morris . . .	59.2	59.0	7.03	0.119
Broyles . . .	59.4	61.0	7.26	0.120
Henderson . . .	71.3	71.0	8.91	0.125
Loewenthal . . .	60.1	59.0	7.38	0.125
Cohn . . .	65.0	62.6	8.05	0.126
Steltz . . .	52.3	53.0	7.13	0.134
Sliney . . .	61.3	60.6	8.39	0.138
Coffman . . .	59.1	58.0	8.17	0.140
Zooman . . .	54.0	55.0	8.25	0.150

¹ In this calculation the figures used for body weight are those of April, or where there is much difference the average of the October and April weights is used.

"We believe that these experiments demonstrate the possibilities of a physiological economy corresponding to a saving of considerable protein food. Aside from its possible economical or sociological importance this may not be without physiological significance. The results are presented as a contribution to the solution of a serious problem. If the data obtained in these experiments, representing a protein requirement 50 per cent. lower than the figures usually quoted as necessary to maintain strength and health, approach with any degree of accuracy to the true *minimal* requirement of the men under observation, we believe that the physiological needs of the body can be served for an indefinite period on a greatly lessened protein metabolism. The fact that the greater part of the nitrogen contained in an ordinary diet, including 120 to 150 grams of protein per day, is speedily eliminated lends favor to the view that it can satisfactorily be replaced by other foodstuffs. As Folin has said: "Nitrogen enough to provide liberally for the endogenous metabolism and for the maintenance of a sufficient supply of reserve protein is shown to be necessary. But it ought to be neither necessary nor advantageous for the organism to split off and remove large quantities of nitrogen which it can neither use nor store up as reserve material.

"In considering the possible physiological advantages of some reduction in the protein element of the standard diet, it will be recalled that many of the disorders of metabolism involve the imperfect katabolism of protein, so that nitrogenous derivatives other than urea are liable to arise. Lowered protein intake, especially diminished meat consumption, means a decreased metabolism of the purins. The diet of the professional group was very deficient in purin compounds as a rule. But even among the other groups when meat was more freely eaten, although in small amounts, the daily output of uric acid rarely exceeded 500 milligrams. It is difficult to see anything other than an advantage in a diminished production of intermediary products of protein disintegration—for example, amino-acids and uric acid—under conditions where they are not properly converted into their appropriate end-products. This involves no assumption of any harmfulness of the excess of ordinary nitrogenous excretives in health. In disease, however, many conditions suggest themselves in which the clinician may do well to consider the therapeutic value of the possibilities involved in the foregoing discussion. This applies particularly to disorders in which the organs of protein digestion (gastro-intestinal tract), metabolism (liver), and nitrogenous elimination (kidneys) are concerned. Furthermore, there is no lack of evidence that temporary *protein* starvation is ordinarily not attended with any *immediate* deleterious effects, owing to a considerable protein reserve in the body; so that the physician meeting with circumstances of disease complicated by the difficulties of the "mechanics" of nutrition, for example, may readily exchange the minimum temporary damage or loss occasioned by endogenous protein katabolism in the absence of food, for permanent therapeutic gains.

"If we pass to the data available regarding the total food demand of the body, expressed in terms of energy katabolized daily, statistics of

actual food consumption show a fairly wide range between 1500 and 4000 large calories. These differences are conditioned in part by differences in the individuals studied, as well as by the variable demand created by unlike degrees of bodily activity. More exact information may be expected from the increasing number of calorimetric observations made directly on man. In general the latter show a utilization of about 30 large calories per kilo of body weight during rest and fasting, increasing somewhat when food is administered, and rising to over twice this amount when muscular work is done. In cases of extreme exertion during many hours of the day, the transformation of energy may increase to 130 large calories per kilo of body weight. Calculated for a man of 70 kilos, the figures range from 2100 to 9000 large calories, the latter representing an extreme, yet not unreachd, figure. To what extent the more usual average metabolism of 3000 calories per day represents the *actual* needs of the body of a 70-kilo man during moderate work cannot be conclusively determined at the present time. From such observations as we have been able to gather in our experiments of lowered protein diet, we are inclined to the view that the customary standards for the total energy demands represent a high rather than a low limit; for such approximate valuations as we were able to give to the diets used in these experiments, and which are here mentioned with due reservation in view of the lack of direct fuel value determinations, indicated a metabolism of energy not greatly, if at all, exceeding 40 calories per kilo of body weight.

"Among the better classes, the nutritive demands are certainly more than satisfied by the customary dietaries. Whether man can live on different nutritive planes, as various physiologists have suggested, remains to be seen. Any complete answer to such a question must take into consideration many factors more general in application than is indicated by bodily equilibrium alone. Mental as well as bodily efficiency, health and vigor must remain unimpaired. Much has been written about the relation of diet to the development and characteristics of races; a review of the literature soon convinces one, however, that it is impossible to form an unprejudiced judgment from the conflicting data, or unconfirmed opinions.

"Muscular activity increases the demand for nutriment; but whether it increases the need for protein seems very doubtful. The final answer will depend upon a determination of endogenous protein metabolism during work, measurable perhaps by the output of creatinin. It is not unlikely that the wear and tear of the contractile tissues will be found somewhat increased by maintained activity. With a surplus of protein in the diet, however, this does not make itself manifest in any study of total nitrogen exchange. As a rule we eat to satisfy the demands of the appetite without considering the true physiological needs of the body, or whether the appetite is in any degree proportional to these. Perhaps the unwitting use of an excessive diet is occasioned by the modern culinary methods which make food palatable and attractive; and the danger in this direction applies more particularly to inactive, well-to-do persons than to the poorer working classes with a large nutritive demand."

Personally the reviser believes the low protein diet has much to commend it. He believes it to be a fact that the great majority of people eat more than they need to secure maximum efficiency. It is, however, no doubt true that there are *two* sides to this question of protein requirement. This is indicated by the following summary of some of the more important arguments *for* and *against* the low protein standard:

Arguments *for* a low protein standard: (1) Ingestion of low protein diet leads to *greater strength and endurance*. The individual is a *more efficient machine* and is free from minor ailments. On the other hand a heavier diet may produce obesity and thus cause less freedom in the movement of important organs (*e. g.*, heart, stomach, etc.). (2) Protein foods are in general *expensive foods*, therefore a high protein diet entails an *economic waste*. The bulk of the nitrogen of such a diet is moreover useless to the organism and is rapidly eliminated. (3) This increased elimination of waste nitrogen as mentioned above has a tendency to *overwork the kidney* and cause lesions of this organ. (4) Low protein ingestion is accompanied by a *decrease in intestinal putrefaction* and a consequent decrease in the absorption of its toxic end-products. (5) High protein diets are selected by many people and races through *force of habit* and not because such diets most satisfactorily fulfil the physiological requirements of the body. (6) One of the best arguments favoring a low protein diet is afforded in the fact that Prof. Chittenden has subsisted for about eight years on a diet "remarkable for its low level of protein intake, and as yet without suggestion of anything but benefit to health and efficiency." He claims that the low protein diet has improved his health, general physical condition and mental power. (See arguments 3 and 10 *against* low protein.) (7) Hindhrie has experimented with low protein diets for seventeen years and concludes that nitrogen balance may be maintained on a protein level fully as low as as that suggested by Chittenden.

Arguments *against* low protein standard: (1) When permitted free choice of food individuals have been found to choose a *high protein* diet. On this point Sir William Roberts says: "The generalized food customs of mankind are not to be viewed as random practices adopted to please the palate or gratify an idle or vicious appetite. These customs must be regarded as the outcome of profound instincts which correspond to certain wants of the human economy. They are the fruit of a colossal experience accumulated by countless millions of men through successive generations—and are fitted to yield to observation and study lessons of the highest scientific and practical value." (2) There is danger of ingesting a diet *too low in energy value* when on a low protein standard. (3) The human body needs a *reserve*. The low protein standard might be satisfactory for a given individual for a short period but unsatisfactory if ingested during the major part of the life of that individual. (See 10 below and argument 6 *for* low protein). (4) The "minimum" is not necessarily the "optimum." Because an individual can exist on a low protein diet is no adequate reason for considering such a condition as the best possible condition for such individual. A man may exist with *one eye, one ear, one kidney*. Nature's foresight in giving us paired

organs is an important "factor of safety" (Meltzer). (5) Low planes of mental, moral and physical development accompany continuous ingestion of low protein diet. (6) High protein animals of "Zoos" are *less susceptible* to tuberculosis than low protein animals. In line with this McCay says, "In India, the home of epidemic diseases, famines or years of scarcity never fail to be accompanied by outbreaks of infections which pick out, with unflinching regularity, those who have become enfeebled from want of proper food." (7) On low protein diet the musculature may be developed at the expense of other parts of the body. (8) Benedict claims that Chittenden's good results were due to (a) mental suggestion, (b) routine of life, (c) regular gymnasium exercise. He says, however, that fecal analysis showed that there was less complete absorption of the end-products of protein digestion from the intestine, thus indicating a disturbance in the alimentary tract. (9) Certain experiments on swine (Shutt) have shown inferior pork to result from the ingestion of a low protein diet. Skinner has further shown an impairment of the digestive function to follow the ingestion of a low protein diet by swine. (10) An observation of Haecker is important when considered in connection with argument 3 given above. "Two groups of cows, ten in each group, were fed for a period of three years; one group on a diet containing the normal proportion of protein, the other on a much lower protein ration. No ill effects appear to have been noticeable for some time, although the second group had lost somewhat in weight. During the first part of the third winter both groups did well, but by January the cows receiving the low protein dietary began to fail. By March 13, it became absolutely necessary to increase the proportion of protein, as the cows had become very thin in flesh and their coats dry and harsh—a well-recognized indication of under-nutrition." (11) McCay as the result of an extended series of studies made in India says: "Those people whose dietary affords a low level of protein metabolism are, so far as our knowledge goes, of poor physique, wanting in stamina, and lacking in the manly qualities that are essential in commanding and retaining the respect of the more virile races. We have no hesitation in saying that among the tribes and races contrasted, the higher the level of protein interchange, the more robust and energetic, and the more manly the race."

INORGANIC MATTER IN NUTRITION

The emphasis placed upon the importance of protein and its associated organic nutrients so far overshadows that customarily placed upon the inorganic side of our dietary that few, except those actively interested in nutrition work, appreciate to the full the importance of the rôle played by these dietary constituents. The laying of great stress upon the importance of protein material as a dietary constituent is perfectly justifiable and firmly founded upon fact. However inorganic matter is also of great importance. Inorganic matter is intimately connected with normal cell function; it constitutes an important con-

stituent of body fluids; it occupies a most preëminent position as an article of diet, and its non-ingestion engenders abnormality of function, with death as the penalty for its continued exclusion from the dietary. It is of importance that all proteins, even the crystalline ones, contain some inorganic matter in their molecule. If this inorganic matter be removed the protein no longer functions as true protein.

That pronounced metabolic disorders follow the non-ingestion of inorganic matter has been clearly demonstrated. Taylor ingested a "salt-free" diet (0.1 gram ash) for a nine-day period, the diet containing satisfactory amounts of protein, fat and carbohydrate and possessing a proper calorific value. At the end of the ninth day it was necessary to terminate the experiment due to symptoms of grave nutritional derangement (acidosis, etc.).

Forster in certain experiments upon dogs demonstrated that the feeding of a diet approximately "salt-free" produced a fatal result more quickly than absolute starvation. Bunge suggested that the lack of inorganic salts may possibly have brought about the fatal result in an *indirect* rather than a direct manner. Protein contains from 0.3 to 2.5 per cent. of sulphur. Now upon the decomposition of this protein within the organism the contained sulphur goes to form sulphuric acid, and this is turn under normal conditions unites with the basic salts of the ingested food and is eliminated from the body. Food from which the inorganic material has been removed of course contains no basic salts to unite with this sulphuric acid. In this dilemma the sulphuric acid seizes upon the basic material of the living tissues and thus promotes pronounced pathological conditions such as acid intoxication or acidosis. In words of Bunge it may be said to "wrench individual bricks out of their places and to thus induce the destruction of the edifice." Lunin, in Bunge's laboratory, made certain experiments on behalf of the above hypothesis. He fed mice a "salt-free" diet *plus sufficient alkali to unite with the sulphuric acid resulting from the decomposition of the protein fed*. He was able to show that life might be prolonged by the neutralization of the acid but that the whole period thus embraced was exceedingly short as compared with the normal life period.

On an ordinary mixed diet the salts may in general be said to consist of three kinds: (1) *neutral inorganic electrolytes*, especially chlorides; (2) *vegetable salts* of the alkali and earthy metals, carbonates, acetates, tartrates, citrates, etc., which are present rather abundantly, and (3) *acid phosphates*, which are present in comparatively small amount. Were the salts of these three types removed from an ordinary mixed diet, then thoroughly mixed and allowed to come to equilibrium, we would find that the reaction would be rather strongly alkaline.

With a single exception such a diet contains a sufficient quantity of inorganic salts to insure normal cell life so far as the inorganic factors are concerned. The one exception noted is *sodium chloride*. Why is it necessary to add sodium chloride and no other salt? The answer has been given by Bunge. He called attention to the fact that numerous experiments have shown that the craving for sodium chloride in the diet is evinced by *herbivorous* animals and never by *carnivorous* ones. Tigers,

lions, etc., have no particular liking for sodium chloride, whereas the wild herbivorous animals are extremely fond of salt. The herbivorous animals need the extra sodium chloride because of the predominance of potassium in their diets, vegetable cells possessing a high potassium content. Why should an increased ingestion of sodium chloride follow excessive potassium intake? The reason follows: The predominating inorganic salt of blood serum is sodium chloride. When a salt of potassium, *e. g.*, the carbonate, is ingested, it comes in contact with sodium chloride, and a consequent reduction in the sodium chloride content occurs through the formation of potassium chloride and sodium carbonate. This, of course, causes a change in the composition of the blood. The blood now contains as much sodium as before, but this sodium is not in the proper combination, *i. e.*, it is not there as a chloride. In its place we have some potassium chloride and some sodium carbonate, neither of which can fulfil the normal function of sodium chloride. Now it is one of the functions of the kidneys to see that the proper composition of the blood is maintained. Therefore, when this sodium carbonate- and potassium chloride-laden fluid is carried to these organs, the kidneys promptly reject the excess of these salts, pass it off by way of the urine and *leave the blood deficient in sodium and chlorine.*

The following table (from Bunge) indicates the range of variation in the constituents of the ash of the most important articles of diet, arranged according to the content of lime.

ONE HUNDRED PARTS OF DRIED SUBSTANCE CONTAIN.

	K ₂ O.	Na ₂ O.	CaO.	MgO.	Fe ₂ O ₃ .	P ₂ O ₅ .	Cl.
Beef	1.66	.32	.029	.152	.020	1.83	.28
Wheat62	.06	.065	.240	.026	.94	(?)
Potato	2.28	.11	.100	.190	.042	.64	.13
Egg-white	1.44	1.45	.130	.130	.026	.20	1.32
Peas	1.13	.03	.137	.220	.024	.99	(?)
Human milk58	.17	.243	.050	.003	.35	.32
Yolk of egg27	.17	.380	.060	.040	1.90	.35
Cow's milk	1.67	1.05	1.510	.200	.003	1.86	1.60

The marked differences in the distribution of important elements among these familiar dietetic articles is clearly shown. Thus, the poverty of cow's milk in iron and the relative abundance of lime are conspicuous. The total quantity of mineral ingredients included in the ordinary diet of the adult and their distribution has been compiled by Gautier, as shown in the table on page 636.

To the 17.43 grams of inorganic substance here accounted for, should be added 7 or 8 grams of common salt which are daily contributed directly to the food, making a total of 25 grams of inorganic compounds. It is estimated that we excrete somewhat more than this quantity. The slight gain is attributable to the sulphuric and phosphoric acids derived from the oxidation of organic compounds of sulphur and phosphorus ingested. It will also be noted that the preponderance of the ingested inorganic compounds is associated with foods of vegetable origin; this applies in particular to specific elements: Potassium, magnesium and phosphates.

INORGANIC SALTS IN AN AVERAGE DAY'S RATION

Food.	Total weight. Grams.	Inorganic salts. Grams.
Bread and pastry	435	3.15
Meats	266	3.40
Milk	150	1.05
Eggs	30	.03
Fresh fruits	90	.45
Fresh vegetables	200	4.15
Dried vegetables	40	1.20
Potatoes	100	1.20
Cheese	12	.80
Sugar	40	
Butter	28	
Wine	650	1.65
Drinking-water	1000	.35
		<hr/>
		17.43

It is claimed that the rôle played by inorganic salts in cell life is principally osmotic. The regulation of the osmotic pressure of the cell fluid as well as that of the intercellular fluid devolves upon these inorganic salts. There is probably also a well-defined specific action exerted by each individual salt although the exact nature of this action cannot be exactly defined. The cell requires certain definite salts in certain definite quantity and substitutions for these cannot be made and the cell maintain its normal activity. We are unable at the present time to obtain accurate data as to the concentration of the various ions which occur in the cells. We may incinerate the cell and analyze the resultant ash, but this procedure will give us, at most, but a crude idea as to the actual conditions before incineration. Such a process will never tell us the nature of the various complicated combinations in which these various ions may have taken part.

Macallum has reported very interesting work upon the distribution of salts in living matter. He believes the main factor in this distribution is *surface tension*. By microchemical studies on the distribution of potassium salts in cells and tissues he shows that "condensation, on interfaces and in surfaces where the tension is low, is a distinct factor in determining the distribution of salts in tissues and cells." He further states that "The forces governing the distribution of salts in ordinary solutions are profoundly modified in tissues and organs by the action of surface tension, which is a very important factor in the processes of secretion and excretion." He lays great emphasis upon the part surface tension plays in determining the inorganic composition of the tissues and in influencing the functions of the organs.

Of all the inorganic constituents of the body the metabolism of calcium is receiving more attention recently than any of the others. It is of well-known importance, of course, in connection with the study of the growth and development of bone, both normally and under such pathological conditions as operate in rachitis, osteomalacia, osteitis deformans, etc. Its importance in pregnancy is also appreciated, the development of the fetus making large demands upon the calcium supply of the mother.

But apart from these, calcium is coming to have a more potent significance in other clinical connections.

The metabolism of phosphorus is also receiving considerable attention of late. Contrary to our former belief we have evidence that lecithin, nucleoprotein, and other phosphorus-containing substances of the animal body may be synthesized in the organism from *inorganic* phosphates. McCollum and Halpin have also demonstrated the formation of lecithin in the body of the hen when the diet contained no lecithin.

The question of acid-forming and base-forming elements in the diet is an important one. In the course of their metabolic transformations the chlorine, sulphur, and phosphorus present in the food will yield acids whereas the sodium, potassium, calcium, and magnesium will yield bases. The normal dietary should be one which would yield at least sufficient base-forming elements to neutralize the acids formed. If these acids are not neutralized by the bases of the diet they must be neutralized by the fixed bases of the tissues. We then have a serious pathological condition which embraces one of the most harmful of the features of acidosis. It is evident that the so-called "ash-free" or "salt-free" diets are "acid-forming" diets of a pronounced type. This is true because no fixed bases are introduced into the body and the sulphur content of the ingested protein will be oxidized to sulphuric acid and this in turn will remove fixed bases from the tissues for its neutralization. It has further been suggested that scurvy may result from the ingestion of a diet low in base-forming elements. In fact Wright, who made a study of scurvy among British soldiers, reports that the disease followed a decreased alkalinity of the blood which resulted from the ingestion of food containing a deficiency of bases, whereas Gautier claims that foods (vegetables) which possess an alkaline ash act as preventives of scurvy and expresses the opinion that the scurvy epidemic during the siege of Paris was due to the exhaustion of the supply of vegetables and not to the use of salt meat (Sherman).

If we wish to strike a balance of acid-forming and base-forming elements in a diet it is first necessary to determine the chlorine, sulphur, phosphorus, calcium, magnesium, sodium, and potassium. We must then calculate the acid equivalent of the sulphur, phosphorus and chlorine and the alkali equivalent of the calcium, magnesium, sodium, and potassium and strike a balance. Of course, in these calculations we assume that the elements named would be completely oxidized in the body. As a matter of fact a small proportion of the sulphur is not oxidized completely, whereas a certain quota of the ammonia is not transformed into urea. The table on page 638 of acid-forming and base-forming elements in common foods is submitted by Sherman and Gettler¹ on the basis of recent experiments. The table indicates that meats and eggs are rather pronounced acid-forming foods, whereas the grain products are acid-formers of a less pronounced type. Milk is a base-forming food, whereas vegetables and fruits are very pronounced base-formers. The reason the fruits, which may be strongly acid, yield

¹ *Jour. Biol. Chem.*, 1912, xi, 323.

an excess of bases on oxidation is due the fact that their acidity is caused by organic acids, present for the most part as acid potassium salts, and these salts on burning yield potassium carbonate or bicarbonate.

Sherman and Gettler are inclined to believe that "in order to obtain the full physiological effect of a balancing of acid-forming and base-forming elements, the foods which contain a marked excess of acid-forming elements should be balanced in each meal by foods in which base-forming elements predominate." In other words not only must a normal diet contain an adequate supply of inorganic matter, but there should also be a quantitative relationship between the two types of inorganic matter, *i. e.* acid-forming and base-forming elements.

EXCESS OF ACID-FORMING OR BASE-FORMING ELEMENTS IN FOODS.

Article of food.	Excess acid or base in terms of normal solutions.			
	Per 100 grams.		Per 100 calories.	
	Acid (cc.)	Base (cc.).	Acid (cc.).	Base (cc.).
Almonds		12.38	1.86
Apples		3.76	5.98
Asparagus81	3.65
Bananas		5.56	5.62
Beans (dried)		23.87	6.92
Beans (lima, dried)		41.65	12.08
Beets		10.86	23.57
Cabbage		4.34	13.76
Carrots		10.82	23.91
Cauliflower		5.33	17.48
Celery		7.78	42.17
Crackers	7.81	1.95	
Eggs	11.10	7.55	
Egg-white	5.24	9.52	
Egg-yolk	26.69	7.08	
Fish (haddock)	16.07	Not calculated	
Lemons		5.45	12.32
Lettuce		7.37	38.69
Meat (lean beef)	13.91	12.10	
Meat (chicken)	17.01	Not calculated.	
Milk (cow's)		2.37	3.44
Oatmeal	12.93	3.23	
Oranges		5.61	10.94
Peaches		5.04	12.20
Peanuts	3.9070	
Peas (dried)		7.07	1.98
Potatoes		7.19	8.63
Prunes		24.40	8.05
Raisins		23.68	6.87
Rice	8.10	3.35	
Turnips		2.68	6.86
Wheat (entire)	9.66	3.25	
Wheat (flour)	11.61	2.70	

If a normal individual be fed a diet in which base-forming elements predominate (*e. g.*, potatoes) and this diet be replaced by one of equivalent fuel value in which acid-forming elements predominate (*e. g.*, rice) there will be an immediate increase in the acidity of the urine and the ammonia excretion. The therapeutic application of these facts is evident in the dietary regulation of phosphaturia and other conditions.

That a growing organism must be supplied with the inorganic constituents necessary for the proper development and organization of the

tissues is self-evident. It is interesting to note that in milk, nature has supplied the infant with an admirable diet in respect to the needs for inorganic constituents. Milk is richer in calcium, so essential to the development of the skeleton, than any other common dietary article except the egg, which in turn is the storehouse of materials furnished to those young which have an extra-uterine development.

The effects of a lack of certain of the inorganic salts in the diet have long been familiar in the case of the adult as well as the growing young. In health, the adult is continually losing inorganic salts, not only so long as they are contributed to the body with the diet, but equally well when there is a deficiency of them in the intake. Experimental observation shows that with adequate nutrition there is, in the full-grown individual, a tendency toward "salt equilibrium." The latter condition is apparently subject to far more extensive fluctuations than is the case with the organic foodstuffs; but it is as yet impossible to frame any general laws bearing on the indirect influences of the inorganic food constituents on the metabolism of the energy-yielding compounds. Animals fed for long periods of time on foods deficient in calcium, but rich in organic nutrients, are extremely susceptible to intoxication with organic acids, like lactic or oxalic acid. Since the latter may be formed at times in the intermediary metabolism of carbohydrates, in certain perversions of metabolism their toxic action may be traced to the lack of neutralizing or "antitodal" (detoxicating) inorganic bases in the diet.

One of the difficulties in arriving at a correct understanding of the metabolism of the inorganic salts arises from a lack of knowledge regarding the channels by which they leave the body. Iron furnishes a good illustration of some of the errors formerly encountered. The failure to recognize the intestinal epithelium as a factor concerned in the removal of iron naturally allowed a false interpretation to be placed on the occurrence of this element in the feces. To the earlier observers, iron in the stools was a direct indication of lack of iron-absorption, particularly in view of the extremely scanty elimination of ferric salts usually noted in the urine during the same period. But the establishment of the fact that the gut may be directly concerned in the excretion as well as in the absorption of iron compounds, made possible a new interpretation of the earlier observations. Iron might be present in the alimentary canal, either owing to failure to be absorbed, or equally well because it had been discharged into this channel, through the epithelial walls. Since iron may be introduced subcutaneously or even directly into the blood current, without producing any marked increase in the output through the urine, while the feces may contain noticeable quantities, the significance of the intestine with reference to the elimination of such elements becomes apparent.

The part which the inorganic salts may play is thus manifold and difficult of interpretation. No energy is set free in their oxidation; yet they may exert most subtle influences, if such examples as the assumed profound physiological function of the iodine present to the extent of a few milligrams in the thyroid glands are to be trusted.

FECES AND THEIR RELATION TO DIET

At one time it was believed that the feces of a normally nourished adult consisted in large part of undigested and unabsorbed food residues. It has long been recognized, however, that such is not the case. It has been established that the organic matter of feces is made up of bacteria, residues of digestive secretions, cellular material from the intestinal walls, and food residues. There is a formation of feces in the intestine of a fasting animal. The fecal output is far less, to be sure, than is that excreted by a well-fed animal, but nevertheless there is a true fecal formation. Fasting feces are composed principally of bacteria, residues of digestive secretions, and epithelial cells. The adult organism has been found to excrete 7.7 to 9.3 grams of feces per day during a seven-day fast, the fecal matter having a nitrogen value of 0.11 to 0.15 gram. The feces output during fasting will vary both quantitatively and qualitatively.

Metabolic Products in Feces.—Many attempts have been made to devise some means whereby the proportion of the feces made up of undigested food residues could be determined. Such data are particularly desirable in connection with the determination of the extent to which any particular diet is "utilized." The name "metabolic products" is used to designate that portion of the organic matter of the feces which is composed of material other than food residues, while the term "metabolic nitrogen" is used to designate the nitrogen content of these products.

In determining the "percentage utilization" of an ingested nitrogenous food it was formerly considered sufficiently accurate to base the calculations upon the total nitrogen values of ingested food and excreted feces, but it is evident that such procedure gives inaccurate values. In order to obtain more dependable data regarding food utilization it is necessary that the "metabolic nitrogen" of the feces be determined and that this metabolic nitrogen be subtracted from the total nitrogen of the feces before the percentage utilization of the ingested food is calculated. The determination of this "metabolic nitrogen" entails considerable labor, and in case the subject of the study be a human, considerable dietary inconvenience. In the first place the daily *total* nitrogen content of the feces must be determined during the feeding of the diet under investigation. This must be followed by the feeding of a *non-nitrogenous diet* which possesses a similar calorific value to the original diet and which will yield a daily fecal output *similar in bulk* to that yielded by the original diet. It is evident that the calorific requirements may be met by feeding fats and carbohydrates. Because of the small bulk of feces yielded by normal amounts of fats and carbohydrates it is becoming customary to maintain the size of the stool by causing the patient to ingest agar-agar in proper amounts (Mendel and Fine). Various "nitrogen-free" diets have been proposed for use in the determination of the "metabolic nitrogen." These include sugar, lard and agar-agar; sugar, butter and agar-agar; potatoes and butter; starch. On a daily diet of 35 grams of sugar, 45 grams of lard, 200 grams of water,

and 10 grams of agar a 6-kilogram dog has been shown to excrete 0.32 gram of metabolic nitrogen per day (Mendel and Fine), whereas a 65 kilogram man on a diet of 320 grams butter, 128 grams sugar, 2100 grams water and 25 grams of agar has been shown to excrete about 0.5 gram of metabolic nitrogen per day (Foster and Hawk).

Fecal Output as Influenced by Diet, Age, etc.—It has been repeatedly shown that the qualitative and quantitative characteristics of the feces depend on the nature of the diet. This has been shown in certain feeding tests. Rubner, for example, fed 689 grams of *bread* and the resulting feces from this ration amounted to 95 grams of moist or 23.5 grams of dry feces. At the second test 1237 grams of *bread* was ingested from which the resultant feces aggregated 109 grams of moist material or 28.9 grams of dried residue. It is clearly set forth from these two experiments that an increase of approximately 80 per cent. in the amount of food ingested produced increases in the moist feces and the dry residue of only about 15 per cent. and 23 per cent. respectively. Some results obtained by Voit are also of interest. This investigator found that an increase of 400 per cent. in the quantity of *meat* fed a dog produced only a 20 per cent. increase in the output of the feces.

When we come to consider a *milk* diet we find a different relation between the ingesta and excreta than that just discussed for meat and bread diets. In the case of the milk diet the resulting fecal mass is found to be almost *directly proportional* to the quantity of milk ingested. An increase in the milk ingestion produces a proportionate increase in the fecal output. From this we are at liberty to conclude that certain of the milk constituents are not capable of absorption from the intestine. These are in large part salts of calcium and of phosphorus. The nitrogen value of the feces is also increased with an increased milk ingestion.

According to Camerer any given diet causes the formation of much less feces per kilogram of body weight in the adult organism than in that of the child. One striking fact was that a child five months of age eliminated approximately nine times as much feces per kilogram of body weight as did a man sixty-six years of age.

The qualitative character of the food as well as its mode of preparation are important factors in influencing the extent of the fecal output. Thus, for instance, milk, cheese, rice, eggs, meat, macaroni and white bread are largely available for the uses of the organism and therefore yield but a comparatively small amount of feces. On the contrary there are other ordinary dietary constituents, among them the cellulose-containing vegetables which do not possess this high availability and therefore yield a much more copious fecal output. An example of the foregoing statement is furnished by the experimentally determined fact that 1435 grams of *meat* have been found to yield but 64 grams of fresh feces, whereas 3831 grams of *cabbage* yielded 1670 grams of fresh feces (Schmidt and Strasburger). In other words in the case of the meat the resulting fecal mass was 4.5 per cent. of the weight of the original food, whereas in the case of the cabbage it was 43.6 per cent. of the weight of the original food. However, notwithstanding this fact, the percentage of dry substance in the meat feces was over six times as great as in the feces passed

after the cabbage diet, the actual figures being 4.4 per cent. for the cabbage diet and 26.9 per cent. for the meat diet.

Relation between Diet and Fecal Nitrogen Values.—We have seen how the quantity of feces formed varies with the character of the diet. This is not true for the *percentage* content of nitrogen, however. In case the diet is made up of a food which is very thoroughly digestible, such for example as meat, rice, etc., the percentage content of nitrogen in the dried feces will not vary to any considerable degree. This is shown by the following data from Prauznitz, which show but slight variation in the nitrogen percentage of the feces of three different individuals ingesting two different diets.

Subject.	Food injected.	Percentage nitrogen in dry feces.
H.	Rice	8.83
H.	Meat	8.75
W. P.	Rice	8.59
W. P.	Meat	8.48
F. Pi.	Rice	8.70
F. Pi.	Meat	9.05

Meat fed.	Percentage nitrogen in feces.
None	7.96
500 grams	6.50
1000 grams	6.50
1500 grams	6.50
1800 grams	6.50
2000 grams	6.50
2500 grams	6.50

The uniformity in the nitrogen percentage in the feces from a meat diet is shown by the data submitted by Müller from an experiment upon a dog. These indicate that as soon as the dog was placed on a meat diet the feces assumed a definite composition (6.50 per cent. nitrogen) and maintained this composition unchanged even when the amount of meat fed was increased fivefold.

Data such as those quoted have been interpreted as indicating that the feces resulting from a thoroughly digestible food are composed principally of “metabolic products.” There is other rather strong evidence to bear out such a contention. For example Voit showed that the material produced in an isolated loop of the intestine of a meat-fed dog was of a similar composition and contained the same percentage of nitrogen as the feces of the normal intestine through which food and its digestion products were passing. When calculated to unit surface the quantity of dry matter present in the isolated loop was very similar to that present in the feces proper. Mosenthal showed that the succus entericus which was secreted into the intestine during the digestion of the diet and the resorption of its digestive products contained from 21 to 43 per cent. as much nitrogen as the ingested food contained, and moreover that this volume of secretion was equivalent to 225 to 607 per cent. of the nitrogen content of the feces. Of course under normal conditions the major quantity of this succus entericus is reabsorbed. Mosenthal places the reabsorbed portion as equivalent to about 25 per cent. of the ingested nitrogen. The equivalent of about 10 per cent. of

the ingested nitrogen is excreted in the feces. Any pronounced or prolonged derangement of the function of absorption is bound to cause a very serious alteration in the "metabolic nitrogen" of the feces.

The feeding of indigestible non-nitrogenous materials has been found to influence the fecal nitrogen values. Some interesting data on this point have been recently submitted by Mendel and Fine. Dogs fed upon a diet of meat and lard excreted an average of 0.19 gram of nitrogen per day in the feces. When three grams of agar and seven grams of bone ash were added to the above diet the daily output of nitrogen in the feces was increased to 0.37 gram. When crude fibre was substituted for the agar and ash the fecal nitrogen value rose from 0.12 gram to 0.28 gram. It is suggested that the feces from a meat diet represent a small portion of the succus entericus which was passed into the intestine, the major quantity of the juice having been absorbed before the rectum was reached. The actual degree of reabsorption of the succus entericus is governed by the rate of peristalsis, and this is in turn influenced by the character and volume of material present in the intestine. If to a thoroughly digestible diet of meat we add an indigestible substance or one less digestible than the meat, we stimulate peristalsis and consequently less metabolic products are reabsorbed and the fecal quota of these metabolic products is augmented. If the indigestible material which is added to the diet be one which contains no nitrogen, such, for example, as agar, crude fibre, or bone ash, we will lower the fecal nitrogen percentage. On the other hand, if the less digestible material be highly nitrogenous, such for example as albuminoid material or certain proteins, then the fecal nitrogen percentage will be raised. We may even have such a mixture of non-nitrogenous and nitrogenous materials of low digestibility as to yield a fecal nitrogen percentage identical with that obtained from the analysis of meat feces. It is not safe to judge of the digestibility of a food substance solely from the standpoint of the fecal nitrogen concentration.

Inorganic Matter in Feces.—The feces of normal individuals contain considerable quantities of inorganic matter, in particular calcium, magnesium, phosphorus, sulphur and iron. The principal avenue for calcium excretion is the feces. Under normal conditions only about one-tenth of the ingested calcium is excreted in the urine. A certain quota of the ingested calcium after being absorbed from the intestinal tract and fulfilling its metabolic function is excreted through the intestinal wall into the lumen of the intestine and subsequently eliminated from the body in the feces. The same is true for phosphorus and iron. In cases of osteomalacia more calcium is excreted in the urine than in the feces. Goldthwaite, Painter, Osgood, and McCrudden submit data from a case of osteomalacia which indicate that in an interval of eight days 3.8 grams of calcium oxide were eliminated in the urine whereas the output by way of the feces was only 1.8 gram. In osteitis deformans the relationship between urinary and fecal calcium is just the opposite to that found in osteomalacia, (Da Costa, Funk, Bergeim, and Hawk). The preponderance of calcium in the feces is much more pronounced than in normal persons. The normal urine-feces calcium ratio ranges

from 1:4.5 to 1:9, whereas in two cases of osteitis deformans the ratios were 1:23 and 1:60 respectively.

Metabolism studies upon adult subjects show that there is more magnesium excreted in the urine than in the feces. The percentage of this element which fulfils its metabolic function and is subsequently excreted through the wall of the intestine and passed out in the feces is probably much less than in the case of calcium.

On a normal phosphorus ingestion about 20 to 35 per cent. of the amount excreted passes out by way of the feces. Some of this is in organic and some in inorganic combination, the latter predominating. Foods rich in calcium or which yield an alkaline ash generally cause an increase in the proportion of phosphorus excreted in the feces. The carnivora excrete phosphorus principally in the urine. The herbivora on the other hand excrete practically all of their metabolic phosphorus through the intestinal wall.

The iron of the ingested food after its absorption from the intestine, passes into the circulation and is carried principally to the liver, spleen and bone-marrow. After fulfilling its function the iron is returned through the intestinal wall and eliminated in the feces.

It is claimed that silicon which has been believed to be eliminated solely by the feces may be eliminated by the urine as well. Schulz claims that the urinary silicon values will range from 0.09 to 0.26 gram per day. It is apparent, therefore, that the silicon derivatives in foods may be absorbed from the intestine and reappear in the urine. It is uncertain just what part silicon plays in human metabolism.

Chlorides because of the ease with which they are brought into solution and absorbed are seldom found in normal feces except in traces.

NUTRITION AND GROWTH

(Rôle of individual proteins, of fats, lipoids, and inorganic matter.)
Through the intervention of the hydrolytic digestive procedures of the gastro-intestinal tract the protein portion of the ingested food is transformed into amino-acids which are, at least in part, absorbed as such and carried to the tissues and deposited until required for nutritional purposes (Folin and Denis; Van Slyke and Meyer). That various proteins differ in the number and character of the amino-acids which they yield upon hydrolysis is well known. This point is shown by the following table.¹

The proteins differ widely as to their content of amino-acids, but we cannot alter the chemical characteristics of any animal tissue by a selective protein dietary. In other words, no matter what proteins we may include in the dietary of a man the cells and fluids of that man possess the same characteristics as they would possess had we used other proteins in the dietary.

¹ Hawk's "Practical Physiological Chemistry."

PERCENTAGE OF AMINO-ACIDS IN PROTEINS

Amino-acid.	Protein.					
	Gliadin (wheat).	Edestin.	Casein.	Gelatin.	Globin.	Zein.
Glycocoll	0	3.80	16.50		
Alanine	2.00	3.60	1.50	.80	4.2	9.79
Valine	3.34	6.20	7.20	1.00	1.88
Leucine	6.62	14.50	9.40	2.10	29.0	19.55
Proline	13.22	4.10	6.70	5.20	2.3	9.04
Phenylalanine	2.35	3.10	3.20	.40	4.2	6.55
Aspartic acid58	4.50	1.40	.56	4.4	1.71
Glutamic acid	43.66	18.74	11.00	1.88	1.7	26.17
Serine13	.33	.50	.40	.6	1.02
Tyrosine	1.20	2.10	4.50	1.3	3.55
Arginine	3.16	14.20	4.84	7.62	5.4	1.55
Lysine	0	1.70	5.95	2.75	4.3	
Histidine61	2.20	2.50	.40	11.0	.82
Tryptophane	1.00	+	1.50	+	
Cystine45	1.00	.0653	?
Oxyproline	?	2.00	.23	6.40	1.0	?
Diaminotrihydroxy- dodecanoic acid75	?

It has been suggested (Abderhalden) that inasmuch as there is no actual evidence tending to show the transformation of one type of amino-acid into another within the animal organism, then the actual building up of protein tissue must be limited by the amino-acid which is present in the ingested food in the smallest relative amount. This view has support in the data from experiments on gelatin and zein feeding, which demonstrate that these "imperfect" or "defective" proteins (from the standpoint of the amino-acids they yield on hydrolysis) are not satisfactory dietary constituents when they are the sole source of the protein fed. As Mendel has said, "Adequate growth has not been observed with any of the various groups of proteins which are, from the chemist's standpoint, notably incomplete." If the view of Abderhalden mentioned above is true, then it should follow that those proteins which most closely resemble the tissue proteins, insofar as their amino-acid content is concerned, should be the most satisfactory from the nutrition standpoint. In other words the products resulting from the cleavage of human tissues should prove more efficient in the up-building of human tissues than should the products derived from the tissues of the ox or sheep. This question as to whether an animal is most efficiently nourished by ingesting the tissues of its own species has been subjected to experimental study. Certain experiments of Michaud apparently show that dogs can be maintained on a minimum level of nitrogen equilibrium through the ingestion of tissues of other dogs. In other experiments it has been shown that the character of the protein made no difference, *i. e.*, the protein of the ox, sheep, or dog was equally efficient so far as the protein minimum is concerned. In this and other connections it should be borne in mind as Osborne and Mendel have said, that "Some proteins lacking one or more of the cleavage products known to be necessary for the formation of the proteins of the animal body are of relatively high efficiency in preventing loss of body nitrogen due to endogenous metabolism, although they are insuffi-

cient for growth." It should further be emphasized that "the processes of replacing nitrogen degraded in cellular metabolism are not of the same character as the processes of growth. It seems also to be a necessary conclusion that the processes of cellular katabolism and repair do not represent a series of chemical changes involving the destruction and reconstruction of an entire protein molecule" (McCollum). What has just been said emphasizes the necessity of differentiating clearly between *growth*, *maintenance*, and *repair*. As Mendel aptly says, "A *man* who maintains his weight may be in excellent nutritive condition, but a *child* which does likewise is failing to grow."

Interesting experiments have been made in which certain "incomplete" proteins (gelatin, zein, etc.) have been fed together with the particular amino-acids which they lack. From the table it will be seen that zein contains no tryptophan, lysin, or glycocoll, whereas gelatin is lacking in tyrosin, tryptophan, and cystin. Experiments of the type mentioned have met with but indifferent success from the nutrition standpoint. On the basis of such evidence as we now have we may say that it seems apparent that the amino-acids, *tyrosin*, *tryptophan*, *phenylalanin*, and *histidin*, are of absolute necessity to the proper nourishment of the animal organism. It will be noted that these amino-acids each contains a carbocyclic nucleus. In fact, the view has been expressed that the animal organism differs from the plant organism in its inability to synthesize cyclic compounds (W. A. Osborne).

That the animal cell may synthesize certain of the amino-acids which are lacking in the diet has been clearly demonstrated. This was first shown for glycocoll. Casein contains no glycocoll, yet animals fed upon this as the sole source of protein have been able to produce far more hippuric acid (after benzoic acid administration) than could possibly be accounted for on the basis of preformed glycocoll in the ingested food or in the body tissues (Magnus-Levy). More recently, Osborne and Mendel have demonstrated that the *gliadins* of wheat and rye as well as the *hordein* of barley suffice for maintenance, without growth. These experiments demonstrate that "the protein of the food can differ very widely in its amino-acid make-up from the tissue proteins of the animal without affecting the well-being of the latter." Although the gliadin diet did not suffice to produce growth, nevertheless the capacity for growth was not lost, and when the gliadin diet was supplemented by another protein containing the amino-acids lacking in gliadin, normal growth resulted.

The relation of the gliadin diet to gestation is of interest. An experiment by Osborne and Mendel demonstrates this: Two white rats were paired and the female placed on a gliadin diet. In one hundred and seventy-eight days she gave birth to a litter of four. These four young rats were satisfactorily nourished by the mother and *grew normally*. After one month three of the rats were removed from the mother and placed upon different diets containing casein, edestin, and milk respectively. The fourth rat remained with the mother. The three rats which were removed grew normally thereafter on their new diets, whereas the rat which remained with the mother began to show a failure to grow

as soon as it began to eat the gliadin food mixture instead of its mother's milk. This experiment affords clear evidence of synthesis by the tissue cells of the mother rat. The gliadin contains no glycocholic acid or lysin. In order to get normal cell construction which accompanies growth these amino-acids must have been synthesized. Moreover, the *nucleic acid* (with its contained content of purin and pyrimidin bases and organic phosphorus) and *casein* of the milk which were not present in the diet (gliadin) which the mother rat had eaten for several months, must be considered as having arisen through synthetic processes. The possibility of intestinal bacteria bringing about the synthesis of amino-acids or the synthesis of protein from non-protein nitrogenous substances is discussed elsewhere. Osborne and Mendel do not consider that the bacterial synthesis entered into the problem in their feeding tests.

In their various feeding experiments with individual proteins such as *casein*, *edestin*, *gliadin*, and *glutenin*, Osborne and Mendel demonstrated that "every animal sooner or later declined when fed with mixtures of isolated and purified protein carbohydrates and fats together with inorganic matter in the form of crystallized salts. In each case immediate recovery followed a change in diet, thus showing the experimental foods to be inadequate for prolonged nutrition." One of the most satisfactory dietary changes was the replacing of the inorganic constituents and a part of the carbohydrate by "protein-free milk." Many experiments are recorded in which animals have made an *immediate* recovery when the "protein-free milk" was substituted as indicated. "Even greater success is manifested in maintenance experiments in which the "protein-free milk" furnished the inorganic constituents of the dietary during long periods of time."

These findings are of importance in connection with the recent experiments of Hopkins who claims to show "that milk as well as other natural food materials, contains a substance or substances which, even in very small quantities, suffices to induce normal and continued growth, for several weeks at least, in rats maintained on artificial mixtures of food substances which are otherwise inadequate for growth." The term "*vitamines*" has been suggested for these substances of unknown character which possess such important nutritional relationships. With the aid of the protein-free milk" Osborne and Mendel have been able to "*maintain* rats for periods equal to practically their entire adult lives on foods containing a single purified protein." This would seem to indicate "that monotony of diet is not necessarily a troublesome factor and is not of such importance in nutrition problems as is usually supposed." More recently Osborne and Mendel have made an artificial "protein-free milk" by uniting "the various ions shown by analysis to be therein into an artificial salt mixture." Satisfactory results have been obtained with this also. With this mixture the authors have been able to make "the first successful feeding experiments in which prolonged growth has been induced with carefully purified isolated food-stuffs and artificial salt mixtures." The simplest food mixtures with which characteristic growth was obtained were composed of protein, starch, sugar, and the artificial salt mixture. This constitutes a food

mixture which is *fat-free* and probably lipoid-free as well. Under the above conditions growth was secured with the following individual proteins: casein, lactalbumin, ovalbumin, ovovitellin, edestin, cannabin (from hempseed), glutelins of corn and wheat, globulins of squash-seed and cotton-seed, glycinin of soy bean and excelsin of the Brazil nut. (*Continued* growth however was brought about only by replacing the diet containing the "protein-free milk" by the "milk food" mentioned in a later connection. In other words the "protein-free milk" invariably fails sooner or later to satisfy the nutritive requirement for growth.) Gliadin of wheat and rye and hordein of rye suffice for maintenance *without growth*.

The satisfactory results following the ingestion of *fat-free* mixtures mentioned above would indicate that fat, under some conditions at least, is not absolutely essential to the dietary. The importance of lipoids in nutrition has been demonstrated by Stepp, who failed to secure satisfactory nutrition on a lipoid-free diet. When alcohol-ether extracts of materials rich in lipoids were added the nutritive conditions improved. The addition of lecithin and cholesterol was not sufficient to cause normal nutrition. It is thus evident that these lipoids are not the only ones essential to life. Very recent experiments of McCollum and Davis have also demonstrated the importance of lipoids (lipins) for growth.

Certain very recent experiments of Osborne and Mendel on the question of growth deserve mention. These experiments emphasize the importance of milk as a growth-promoting food. Young rats fed upon a specially prepared "milk food" (a paste consisting of milk powder, 60 per cent.; starch, 12 per cent.; lard, 28 per cent.) grew to full maturity and gave birth to litters of "normal young which in turn have thriven on diets precisely like that furnished to their parents." Such tests show that the milk food contains all that is essential for *both maintenance and growth*.

These investigators then prepared an artificial milk food from purified protein, lard, starch, and "protein-free milk." One such food mixture had the following composition: edestin (18 per cent.), starch (26 per cent.), lard (28 per cent.), "protein-free milk" (28 per cent.). Growth was secured by means of this artificial milk food, but the growth was not prolonged. Capacity to grow ceased in about one hundred days and a change in diet was necessary or the animal declined and died. It is evident then that the " 'protein-free milk foods' are deficient in or completely lack something which milk contains and which is indispensable for perfect growth." If such animals be given the milk food (paste) prompt recovery and continuation of normal growth are observed. The authors say, "We have already noted that ultimately failure inevitably ensues when rats furnished a diet containing an adequate protein and 'protein-free milk' have made a considerable portion of their natural growth at a normal rate. Since no such failure to grow is observed when young rats are fed with the milk food, and since also those that have ceased to grow on the 'protein-free milk' diet or have declined are promptly restored to satisfactory conditions of growth by the use of milk, it is evident that the latter contains something which our

'protein-free milk foods' lack. It seems probable that the missing substance is organic in nature, for the 'protein-free milk' may be presumed to contain all of the inorganic constituents of the milk. Nevertheless, in view of the limitations of our knowledge regarding minute quantities of elements which may play an important part in nutrition, hasty generalizations in this direction are scarcely permissible." In this connection mention is made of the fact that better results were obtained with "artificial protein-free milk" whose inorganic constituents were made up from "commercial" chemicals than were obtained when chemicals of a high degree of purity were used. The better results may have been due to the presence in the commercial chemicals of minute traces of some contaminating element. The authors subsequently prepared an artificial "protein-free milk" which contained traces of various elements (iodine, manganese, fluorine, aluminium) which have been found in traces in animal tissues. This new preparation yielded considerable growth which in most instances ceased sooner than that induced by the natural "protein-free milk."

Osborne and Mendel have attempted to find out what the essential accessory factor is which is present in the "milk food," and gives it its greater growth-promoting properties as compared with "protein-free-milk food." They studied first the nutritive influence of cream (butter). From these experiments they concluded that there is present in butter a substance exerting "a marked influence upon growth," and furthermore that "this substance is largely, if not wholly, removed in the preparation of our 'protein-free milk' ". This explains the greater nutritive efficiency of the "milk food" over the "protein-free milk food."

Aaron has attempted to learn by experiment whether or not it is possible to cause a complete suppression of growth by means of dietary restriction and if so for how long a period. Several groups of dogs were used in his tests. One group received just enough food to maintain a constant body weight, whereas others were fed different amounts of food additional in order to produce varying rapidity of growth. Aaron demonstrated that if the body weight of a growing dog be kept constant or slightly decreasing, the bones continue to grow and increase in weight. This bone growth, however, is less rapid than in a normally nourished dog. The bones have evidently grown at the expense of certain other parts of the body, since the body weight has remained constant. By means of tissue analysis it was learned that the fat deposits and muscles (protein) of the underfed animals had been depleted. The brain was of approximately the same weight as that of a normal animal. This is significant in connection with certain cases of infantilism in which children show marked mental development in spite of retarded growth.

The experiments of Waters on growing cattle are also of importance. This investigator demonstrated that ungrown animals that had previously been well nourished continued to increase in height and in width of hip, even though on a starving ration. It seems then that the animal body is able to draw for a protracted period and to a pronounced degree on its reserves for the purpose of growth. Waters' experiments indicate that "after the reserve is drawn on to a certain extent to support growth,

the process ceases and there is no further increase in height or in length of bone." From then on it is a question of maintenance.

That different food mixtures although equal in nutritive value according to current ideas do not always comport themselves similarly in nutrition has been demonstrated. Certain experiments of McCollum, Hart, and associates show this. It was found, for example, that "calves fed three years on wheat did not develop as well as the control animals fed on rations of oats or corn in quantities of equal nutritive value." It is not plain at this time just what is the reason for this nutritional phenomenon. It may be due to the divergent character of the protein or it may be due to the fact that wheat is lacking in some constituent which is essential to the most economical nutrition.

The influence of growth on metabolism deserves careful investigation, and a study of the nutritive changes in the young is certain to afford an abundance of practical suggestions. The available data indicate a fairly good absorption of the foodstuffs in young infants, the figures for the total available energy varying from 90 to 96 per cent. of the total intake. Sugar absorption appears to be by far the most perfect. Oppenheimer first called attention to the fact that the gain in weight of infants is directly proportional to the quantity (or calories) of milk ingested.

It is noteworthy that the appetite determines the regular ingestion of sufficient energy for the life processes, plus a small but fixed extra percentage necessary for growth. Lusk has formulated a law of growth, that in the development of the normal young of the same age and species, a definite percentage of the energy content of the food is retained for growth irrespective of the size of the individual. According to Heubner, vigorous growth in infants demands an intake of energy amounting to 100 to 120 large calories. That growth itself is attended with an active chemical exchange is shown by studies on the respiration of the embryo, in which the gas metabolism has been found to be as active as that of adults. The metabolism of the young appears to be somewhat more active than that of the adult. Although it appears as if the metabolic processes are less extensive in *old age*, it must be remembered that the activity of the individual is greatly diminished, and our conclusions are based upon the dietetic habits of the old rather than on actual metabolism experiments. It seems doubtful if any specific influence of old age aside from diminished muscular exertion can be demonstrated.

Influence of Climate, Altitude, Temperature, etc., on Metabolism.—The explanation for many of the undoubted effects which external *climatic* and *hygienic* conditions impose upon metabolism is not yet forthcoming. In some cases, problems of temperature regulation seem to be concerned; for the temperature, relative humidity of the air, and its rate of movement modify the "physical" regulation of the body temperature so long as an excess of heat is produced in metabolism. But below the so-called "critical temperature" (about 37° C. for naked man, according to Rubner, and 15° C. in ordinary clothing) the incidental heat production no longer suffices to maintain the normal temperature of the body, and additional body material must be oxidized for this special purpose. Under ordinary circumstances this is avoided by the devices used to keep our

immediate surroundings above the point where a "chemical" or metabolic regulation of temperature is called into play. Herein lies the indirect influence of *clothing* on metabolism. We are accustomed to dress ourselves in such a manner as to make the loss of heat equivalent to that which the naked body would undergo at about 33° C. The *cold bath*, rapidly removing heat from the body, stimulates katabolism.

Lately, the action of *high and low altitudes* has received considerable attention in connection with climatotherapy. It appears that both mountain- and sea-air may exert a stimulating influence upon metabolism in those unaccustomed to the climatic condition selected. This is made evident in the increased consumption of oxygen and output of carbon dioxide at rest without food. It has become quite certain that other climatic factors than the diminished barometric pressure are effective in the case of mountain experiences and similar subtle influences appear to come into evidence at the seashore.

MISCELLANEOUS MATTER OF NUTRITIONAL INTEREST

Defensive (Protective) Enzymes and Serodiagnosis.—Through the important researches of Abderhalden we have come to recognize a class of enzymes called *defensive (protective)* enzymes. This investigator has made an extensive study of the way in which the animal body *defends* or *protects* itself against foreign substances. Under normal conditions no foreign substances which require rapid cleavage enter the blood. In case such substances find their way into the circulation they are useless and often directly harmful to the tissue cells. Realizing this fact Abderhalden attempted to determine whether any new enzymatic properties were acquired by the blood-plasma upon the parenteral introduction of foreign substances into the animal body. In the course of his experiments he injected various protein substances into dogs and rabbits and was able to demonstrate that the plasma of the animals so injected rapidly assumed protein-splitting power but remained inactive so far as fats and carbohydrates were concerned. Evidently a defensive proteolytic enzyme had been manufactured by certain cells (perhaps the leukocytes) and passed into the circulation in order that the foreign protein might be removed by a digestive procedure. On the other hand the injection of sucrose was followed by the appearance in the plasma of an enzyme (sucrase or invertase) capable of inverting the sugar. This enzyme appeared in *fifteen minutes* after the sugar was injected. A defensive lipolytic enzyme was also demonstrated after forced feeding had caused the passage of unchanged fat into the blood.

It has been found that the reaction of the body to foreign substances in the circulation is not limited to substances which may be introduced *from without*. For example certain biological processes *within* the body may cause the production of substances which are just as truly "foreign" insofar as their relationship to the blood is concerned, as are similar substances introduced parenterally. If such substances make their way into the circulation they may produce a response fully as marked

as that brought about by the introduction of foreign material from the external world.

On the basis of the above facts Abderhalden has suggested a biological test for the diagnosis of pregnancy. The blood of a pregnant organism contains cells from the chorionic villi. These constitute a foreign substance (protein) and the body immediately takes measures to free itself from it. A defensive proteolytic enzyme is immediately formed and this enzyme digests the foreign protein. Its action is absolutely specific, it having no power to digest proteins other than those of placental origin. It is claimed that the enzyme is present in the blood from the sixth week after the last menstruation until the end of the third week postpartum. The enzyme is also present in cases of extra-uterine pregnancy. Animal experimentation has shown that a positive reaction may be obtained within twenty-four hours after the ovum is implanted.

Defensive enzymes should not be confused with *anti-enzymes*. Defensive enzymes have a true digestive function, whereas anti-enzymes exert an inhibitory influence which prevents a true enzyme from exerting its normal function. Certain anti-enzymes, such as anti-pepsin and anti-trypsin (if they really exist), exert a *protective* influence in preventing the enzymes, pepsin, and trypsin from digesting certain portions of the gastro-intestinal tract. They are not, however, to be classed as *protective enzymes*. In his very recent writings Abderhalden gives preference to the term *defensive enzymes* (abwehrfermente) rather than *protective* or *defensive enzymes* (schutzfermente), inasmuch as certain enzymes of this character in their attempt to rid the body of some foreign material may produce end-products which are more toxic than the substrate.

Nutritional Relationships of the Intestinal Flora.—The intestine of the newly-born is sterile but this condition is quickly altered and bacteria may be present in the feces after or before the first ingestion of food. The ingestion of mother's milk by an infant tends to reduce the number of species of bacteria present in the intestine and to cause the flora to be made up almost entirely of the *Bacillus bifidus* of Tissier.

It is apparent then that the food exerts an influence upon the intestinal bacteria. This is further shown by the fact that the flora of the intestine becomes richer in species upon the substitution of cow's milk for that of the mother in infant feeding. Even in the adult organism the diet alters to a marked degree the character and extent of the intestinal bacteria. Because the character of the intestinal flora may be somewhat controlled by the nature of the diet we are enabled to regulate the flora to a degree and to substitute useful species of bacteria for those of an undesirable character. However, our knowledge in this regard awaits development to a large extent.

The number of the species of bacteria met with in the feces is very great. However, the more important organisms which may occur there are *B. coli*, *B. lactis aërogenes*, *Bact. Welchii*, *B. bifidus*, and *coccal forms*. The number of bacteria excreted in the feces per day by a single individual is very great. Strassburger places the daily excretion at 128×10^{12} . MacNeal and associates, on the basis of data from a very extensive investigation, place the daily output of bacteria by way of

the feces at 33×10^{12} . Although immense numbers of bacteria are excreted daily in the feces the major portion is made up of *dead* bacteria. It has been estimated (Klein) that 99 per cent. of the fecal bacteria are dead. This value is probably somewhat too high. It is exceedingly difficult to arrive at accurate conclusions regarding the proportion of the fecal bacteria which are dead. The number of living microorganisms in the feces in protracted constipation is sometimes exceptionally small (Herter). MacNeal and Chase have recently shown that "the normal duodenal fluid during a fast is almost free from living microorganisms." In various gastro-intestinal disturbances they found the number of cultivable microbes in the duodenal fluid to be much increased.

The actual weight of the dry bacterial cells excreted daily in the feces has been determined by a few investigators; the amounts vary from 5.34 to 8.54 grams. The output of fecal bacteria has been found to undergo considerable decrease when large volumes of water are taken with meals (Fowler and Hawk; Mattill and Hawk).

It is rather surprising to note the considerable proportion of the dry feces which is made up of bacterial cells. The values vary from 8.67 per cent. to 29.94 per cent. In the case of a fasting man, it has been shown that while the actual output of dry bacteria was very low (0.92 gram daily) the percentage of dry bacterial cells in the total daily excretion of dry feces was 38.62 per cent., a value considerably *above normal* for this individual (Blatherwick and Hawk). The bacteria in the *duodenum* of fasting men are for the most part *dead* bacteria (MacNeal and Chase).

It has been demonstrated in recent experiments that about 50 per cent. of the nitrogen of the feces is *bacterial nitrogen*. In other words one-half of the nitrogen which at one time was considered to be "food residue nitrogen" is in reality nitrogen in the form of bacterial cells. We may, in a general way, consider the bacterial nitrogen of the feces as an inverse index of the relative availability of the diet. The bacteria of the intestine, of course, develop upon the digestion products of protein (in food and secretions) and peptone is the most satisfactory medium for one of the most prolific of the intestinal species, that is, *B. coli*. It is evident therefore that delayed absorption resulting from any cause, thus permitting the protein digestion products to remain for an unusually long time in the gut, will be accompanied by a rapid growth of the microorganisms present. Delayed or faulty absorption therefore yields a high content of bacterial nitrogen in the feces. On the other hand if the absorption processes are stimulated by any means, thus limiting the period during which the products of the digestion of protein remain in the intestine, the material is not at hand to cause the customary growth and development of the intestinal flora. Under these conditions the feces possess a low content of bacterial nitrogen. The stools may contain just as many bacterial cells per milligram of feces, but they are poorly nourished cells and therefore individually they yield less nitrogen than do the bacteria contained in feces which are evacuated under less satisfactory absorption conditions.

Recent experiments have indicated the possibility of the transfor-

mation of nitrogen from certain non-protein sources into protein nitrogen through the intervention of intestinal bacteria. Various synthetic processes which take place in the intestine have also been ascribed in part of these microorganisms. In the case of herbivora non-protein nitrogenous substances (alkaloids, nitrogenous glucosides, amino-acids, amids, phosphatids, nitrates, ammonium, salts, etc.) are important articles of diet. They occur in smaller quantities in the human dietary. The question as to whether these non-proteins furnish energy and are of value for maintenance and growth is an important one. So far as ruminants are concerned, Armsby has the following to say: "A conversion of non-protein into protein appears to be effected by the microorganisms of the digestive tract. The extent of the conversion appears to be relatively greater in the case of ammonium salts and asparagin than in that of vegetable extracts. The protein formed thus from non-protein seems to be digested subsequently." This same investigator further says: "By means of its conversion into bacterial protein, the non-protein of feed may serve indirectly for maintenance and also as a source of protein for milk. The limiting factor in the indirect utilization of the non-protein of the feed appears to be the extent to which it can be converted into protein in the digestive tract rather than any inferior nutritive value of the protein thus formed as compared with that originally present in the feed." It has been clearly demonstrated that the animal organism has the power to build up body proteins out of the amino-acids resulting from the digestion of such proteins.

Osborne and Mendel have also called attention to the possibility of the alimentary bacteria furnishing some of the essential components not present in the ingested food. By means of their synthetic ability these microorganisms perhaps construct new amino-acids from other material. In this way it might be possible for the intestinal bacteria to produce amino-acids which are essential for proper nourishment but which may not result from the cleavage of the protein portion of the ingested food.

Amino-acids in Metabolism.—Experiments of Loewi, Henriques and Hansen, Abderhalden and others have indicated that the animal body may be satisfactorily nourished by the elimination of a whole or part of the protein of the diet and the replacement of the protein by the digestion products of protein, *i. e.*, amino-acids. The recent experiments of Folin and Denis, Van Slyke and Meyer, Buglia, and Dobrowlskaja upon protein assimilation make the above experiments easy of interpretation. According to these experiments the ingested protein is split into amino-acids in the intestine and these are absorbed unchanged and carried by the blood to the various tissues where they are utilized. If, therefore, amino-acids are introduced into the animal body they are carried to the tissues and used in a manner analogous to the utilization of the amino-acids formed in protein digestion in the intestine. One of Abderhalden's experiments deserves mention. He fed a dog for over three months on a diet in which amino-acids constituted the whole source of nitrogen (trace of creatin and creatinin). Sugar and fat were fed in proper amounts to secure satisfactory energy value. The dog gave

evidence of satisfactory nourishment and gained in weight. This experiment also furnishes an excellent example of the power of the animal organism to *synthesize protein*. Evidence of this follows: At the commencement of the experiment the dog was clipped and 76 grams of hair, composed principally of the highly nitrogenous (16 per cent.) protein keratin obtained. At the end of three months the dog had grown a complete coat of new hair. The animal received no protein in its diet and yet was able to form this complex protein of the hair substance. This protein must have been synthesized by the animal cells.

The hippuric acid $C_6H_5CO.NH.CH_2COOH$ in human urine originates in part at least from aromatic substances derived from the diet, especially fruits and vegetables. Benzoic acid is speedily effective in bringing about the synthesis, and a small part may be formed indirectly through putrefactive processes in the intestine. The place of synthesis appears to be principally in the kidneys. The glycocholate required to conjugate with the aromatic radical is derived from proteins. In fasting animals repeatedly fed with benzoates, the amount of glycocholate eliminated through the urine as hippuric acid (benzoyl-glycocholate), compared with the total nitrogen metabolism, indicates that 4 grams of glycocholate may be derived from the metabolism of every 100 grams of body protein. The glycocholate excretion runs parallel with the protein destroyed. Feeding carbohydrates does not increase the formation of glycocholate; but the proportions formed after feeding gelatin and casein are between 3 and 4 per cent. of the protein metabolized. The formation of glycocholate in the body is unquestioned, and the significance of the hippuric acid eliminated is therefore connected with the origin of the benzoic acid.

Of the sulphur compounds in the urine, the ethereal sulphates represent vehicles of elimination for different conjugated groups. In indican, the organic radical is derived from indol formed by intestinal putrefaction from the tryptophan group in the proteins. In accordance with this view, Underhill has found that after feeding gelatin (which contains no tryptophan group) in place of ordinary proteins, the excretion of indican is greatly diminished. The ethereal sulphates also represent other organic radicals like phenyl and cresyl. The immediate source of all these components is not yet established. The inorganic sulphates appear to follow the fluctuations of urea, the neutral sulphur on the other hand showing a possible connection with some endogenous protein katabolic process.

Pathology has furnished several illustrations of perverted metabolism of proteins, which throw some light on the character of the normal intermediary changes. In *alkaptonuria*, the usual destruction of the aromatic protein cleavage products, tyrosin and phenylalanin, appears to be interfered with.

That the "*alkapton*" substances owe their origin to the aromatic group of the protein molecule is evident from the proportionate relation between homogentisic acid and protein destruction, and the fact that the quantity of the acid eliminated after a diet of some specific protein substance is generally equivalent to the amount of tyrosin and phenylalanin yielded by it. Furthermore, feeding of tyrosin and phenylalanin

to patients with alkaptonuria is followed by increased output of homogentisic acid, whereas in normal individuals these aromatic amino-acids are completely burned up. The experimental evidence gives no support to the idea of an *abnormal* production of homogentisic acid from proteins in this disease; but rather that the katabolism of the aromatic complexes ordinarily proceeds through the stages above described, and in alkaptonuria meets with a condition where the final cleavage of the benzene ring represented in homogentisic acid is no longer possible. Accordingly, the healthy individual readily burns up ingested homogentisic acid, while in alkaptonuria it is excreted unchanged.

Cystinuria furnishes another pathological condition which consists in an inability to burn some of the amino-acids formed in intermediary metabolism, notably the sulphur-containing complex of the proteins represented by cystin. When this compound is fed to healthy individuals in quantities as large as 8 grams, it is completely oxidized and the sulphur is eliminated in the form of sulphates and thiosulphates. It may in part be converted into taurin and enter into the composition of the bile as taurocholic acid. The relation of proteins to the production of bile salts thus becomes clear in the case of glycocholic and taurocholic acids, since the origin of glycocoll and taurin in the intermediary metabolism of protein is understood.

Normally, urine is free from cystin even when the latter is fed; but when cystin is given to cystinuric patients it may be in part excreted again. There is at present some divergence of opinion on this point. It is further claimed that cystin is not the only amino-acid which is not burned in cystinuria; in some cases it has been reported that ingested tyrosin and aspartic acid are excreted unchanged. The diamino-acids take a peculiar position in the metabolism of some of the cystinuric individuals. They are partly split up with liberation of carbon dioxide and reappear as diamines. It is likely that this change is attributable to the action of intestinal bacteria, so that the diamines are absorbed as such from the intestine and eliminated unchanged. This seems the more probable because the diamines here concerned, putrescin and cadaverin, have been produced experimentally by the action of bacteria upon the diamino-acids, arginin and lysin, and the diamines are found in the feces as well as the urine in cystinuria. Arginin is doubtless first converted into urea and ornithin, which in turn is transformed into putrescin and carbon dioxide. The interesting cases of cystinuria and diaminuria frequently found combined in the same individual, give further evidence of stages through which proteins presumably may pass in their normal katabolism, and at which the decompositions may be arrested in pathological conditions. Doubtless there are varying degrees of incapacity for the katabolism of proteins in different patients, just as we have different degrees of inability to burn sugar in diabetics.

Water in Metabolism.—It is a fact well-established and old that water is of prime importance to the animal body. For example, every tissue and organ of the body possesses a high water content and the lowering of this is accompanied by a decreased functional efficiency. Water, moreover, forms the basis of all secretions and excretions of the

body. Thus the various enzymes, intracellular and extracellular, operate only when in solution and water forms the medium by which this solution is accomplished. Likewise water operates in an important way in bringing waste products into solution and aiding in their elimination from the body. It is also of importance in the dissociation of chemical compounds within the body. Digestion and absorption are carried out more efficiently in a definite dilution and again it is water which is the ultimate source of such dilution. Water also assists in temperature regulation through evaporation. The statement that *water is indispensable* summarizes the matter. The water content of various tissues and secretions is indicated in the following table.

WATER CONTENT OF TISSUES, SECRETIONS, AND EXCRETIONS

Name.	Water content. Per cent.
Saliva	99.5
Bile (hepatic cells)	98.7
Pancreatic juice	98.5
Gastric juice	97-98
Brain of fetus (gray matter)	92.0
Blood plasma	91.8
Milk	87.0
Brain of adult (gray matter)	84.0
Muscle	75.0
Animal cells	75.0
Feces	75.0
Human body (adult)	63.0
Tendon	62.9
Ligament	57.6
Cartilage	54-74
Bone	14-44
Teeth	10.0
Adipose tissue	6-12
Enamel2

Appreciating the great importance of water many investigations have been made to demonstrate the influence of a decreased or increased water ingestion upon metabolic processes. Because of the important rôle played by protein in the dietary the early experiments, and the majority of the later ones as well, concerned themselves with the influence of water upon the processes of protein metabolism. On the basis of a large number of experiments, it seems evident that an increase in the water ingestion produces an *increase* in the nitrogen excretion. At the same time data have been recorded which indicate that an increased water ingestion produces *no increase* in the output of nitrogen, and one unique study is reported (Roux) in which a claim for a *decreased* nitrogen excretion following high water intake is made.

There are two possible sources of the increased nitrogen excretion observed after increased water ingestion. It might theoretically arise through the "washing out" of nitrogenous metabolic end-products or it might arise from the direct katabolism of protein tissues. Until comparatively recently there was no absolutely definite evidence favoring either of the above hypotheses, although both were vigorously defended by different investigators. Recent experiments made in the writer's

laboratory (Fowler and Hawk; Wreath and Hawk; Wills and Hawk; Fairhall and Hawk; Howe, Mattill and Hawk) apparently furnish proof that the increased nitrogen output following high water intake is due to a *stimulation of protein katabolism*. The most important evidence is the fact that an increase from 700 cc. to 2100 cc. in the daily water ingestion of a dog which had fasted for fifty-nine days caused an increased output of total purin nitrogen (purin + allantoin) in the urine. Inasmuch as the animal received 700 cc. of water on each day of the fifty-nine-day fast, it must be conceded that the tissues of the animal were thoroughly "flushed out" and that the increase in purin nitrogen noted could arise only from actual disintegration of protein tissue. Other evidence is furnished in an increased allantoin output by a man accompanying an increased water ingestion. If we accept Lefmann's hypothesis that a decrease in the creatinin excretion indicates a stimulated katabolism of protein material our finding of a lowered output of creatinin in the periods of high water intake are also significant. Moreover, if we consider creatin as an index of muscle disintegration then the presence of creatin in the urine of our subjects who had received an increased water ration furnished further evidence favoring protein katabolism as the source of the increased nitrogen output so secured.

The drinking of fairly large volumes of water is considered by most members of the medical profession as an advantageous dietary procedure for normal individuals. However, it is sometimes stated that this extra volume of water should never be taken *with meals*, and one of the staple arguments for the non-ingestion of water at meal-time has been the direful results which follow the *dilution of the gastric juice*, which has been supposed to be due to this increased imbibition. This argument can no longer be given consideration according to Foster and Lambert, who report experiments which demonstrate that the entrance of water into the stomach does not produce a dilute gastric juice of lowered acidity, but rather that the entrance of the water acts as a distinct stimulation to the gastric secretion and that the juice, although secreted in larger volume than previous to the entrance of the water, nevertheless shows a higher concentration of acid than does that juice which is secreted under ordinary conditions. The stimulation of the gastric secretion by water has also been demonstrated in certain experiments in the writer's laboratory (Wills and Hawk). In these tests there was an increased excretion of urinary ammonia coincident with the ingestion of increased volumes of water. In view of the fact that acid ingestion or the normal (protein katabolism) or pathological (diabetic acidosis) production of acid in the body (Müller) is accompanied by an increased ammonia elimination, the observation that water drinking with meals is followed by a heightened ammonia excretion is interpreted as indicating an increased production of hydrochloric acid due to a stimulated gastric function.

That the ingested food is more economically utilized when water is taken with meals (Fowler and Hawk; Mattill and Hawk) and that this improved utilization is accompanied by the inhibition of the growth of intestinal bacteria (Blatherwick and Hawk; Mattill and Hawk), a

decrease in the intensity of the processes of intestinal putrefaction (Hattrem and Hawk; Sherwin and Hawk) and an improved liver function have also been demonstrated. It has furthermore been shown that the saliva is a more efficient amylolytic agent when diluted with seven volumes of water (Bergeim and Hawk). In most of the above-mentioned experiments *softened* water was used.

In all the varied experiments from the writer's laboratory in which the theme has been the influence of water drinking *with meals* upon the animal body the subjects have invariably been *normal* subjects, and the results obtained have just as invariably been desirable results. In other words the ingestion of increased quantities of water at meal-time has never been accompanied nor followed by any untoward phenomena of any character whatsoever. For patients possessing lesions of the circulatory or excretory systems (heart, kidney, bladder, etc.) the ingestion of large volumes of fluid at meals is generally considered harmful.

Even in such cases the usual good effects as regards salivary and gastric secretions; intestinal bacteria, putrefaction and food utilization would no doubt be in force as in normal persons, but the possible injury which might result from the passage of the augmented volume of fluid through the circulatory and excretory systems would more than counterbalance the good offices mentioned. It appears then that normal persons may ingest water (*ad libitum*) with meals, whereas those abnormal individuals who possess lesions of the heart, kidney, etc., should have their fluid intake regulated.

It is frequently said that the ingestion of *distilled* water, on account of its lack of salts, has a harmful influence upon the animal body. Findlay speaks as follows on this proposition: "If tissues or cells are placed in distilled water, passage of water into the cells occurs owing to the difference of osmotic pressure. The cells swell up and may finally burst and die. A similar poisonous action on cells is observed when distilled water is drunk. In this case the surface layers of the epithelium of the stomach undergo considerable swelling; salts also pass out, and the cells may die and be cast off. This may lead to catarrh of the stomach. It is to this action of pure water that the harmful effects of melted snow or ice are due, since freezing purifies the water. For this reason, also, one of the springs of Gastein has come to be known as the Poison Spring, although its water is purer than ordinary distilled water." Moreover, the opinion has been expressed (Koeppé; Harlow) that distilled water ingestion leads to catarrh of the stomach. However, Nocht and also Winkler have cited several cases in which prolonged ingestion of distilled water was unaccompanied by any harmful influences. Very recently experiments have been reported (Oehler) which indicate that hemoglobinuria follows the ingestion of distilled water. White mice were the subjects of the tests and the water was introduced into the stomach by means of a syringe. Under these conditions a slight hemorrhage produced might have resulted in the presence of blood in the urine. Otherwise it is a little difficult to see how the hemoglobinuria could have resulted. The introduction of distilled water directly *into the circulation* will, of

course, result in a transient hemoglobinuria; the introduction of the water *into the stomach* is an entirely different proposition.

Experiments in the writer's laboratory have shown that the ingestion of *distilled* water at meals by *normal* men is followed by a stimulated gastric function, decreased growth of intestinal bacteria, lowered intestinal putrefaction and a satisfactory utilization of the ingested nutrients.

If we grant the validity of the claims of Findlay and others above mentioned as to the pernicious influence of drinking distilled water it is apparent that the contentions as advanced by these men cannot be advanced as an argument against the drinking of distilled water *with meals*. The distilled water would cease to function as distilled water soon after its entrance into the stomach, because of the electrolyte content of the average diet. If distilled water is to be considered as having a toxic influence upon the gastric mucosa, such toxic effect must of necessity be more pronounced when the distilled water is introduced into an *empty stomach*. An argument against this supposed toxic action is contained in one of our fasting experiments (Howe, Mattill and Hawk). In this instance a dog was fasted one hundred and seventeen days, receiving 700 cc. of *distilled water* per day. After an interval of normal feeding, the animal was restored to his original body weight and again fasted for one hundred and four days. The organs and tissues of the animal were then examined and no evidence of a deranged gastric mucosa was found. If the toxic influence of distilled water is as pronounced as some would have us believe, certainly a period of one hundred and four days is a sufficiently long interval in which to demonstrate such influence, particularly in the case of a fasting animal.

As a final argument in favor of distilled water ingestion may be cited the fact that this fluid has formed the *chief* beverage of *most chemists* from the time this purified water was first employed in chemical procedure, and so far as known no harmful influence has been recorded.

Fletcherism vs. Food Bolting.—Proper mastication of food is considered to be a necessary preliminary to the most satisfactory digestion of that food. When we inquire as to what constitutes "proper" mastication we are confronted by conflicting views. On the one hand we are told that the salivary secretion is of very little digestive importance, its chief function being to moisten the food and aid in its passage to the stomach (Bunge). This being true it is unnecessary to devote any undue time to the comminution of the food in the oral cavity. On the other hand we are confronted by a body of "hypermasticationists" headed by Horace Fletcher. These tell us that ingested food should be masticated until automatically carried down the œsophagus by the "swallowing impulse." They further postulate that "hypermastication" tends to diminish the amount of food consumed since "the more perfectly a food is chewed the more perfectly is it digested and the more economically is it disposed of in the system" (Campbell). Many eminent nutrition experts (Chittenden and others) have also expressed the opinion that thorough mastication, by causing a fine comminution of the food particles, is a material aid to their further digestion which is to take place in the stomach and intestine.

The habit of rapid eating has no doubt many times been the cause of chronic alimentary disorders. We do not believe, however, that rapid eating will cause such disorders in all individuals. It is a question of individuality. So far as the knowledge of the writer goes, there is no experimental evidence which shows that the human body is more wasteful of protein food introduced by the bolting procedure than when similar food is carried down the œsophagus by the "swallowing impulse" following active overmastication. So far as we are aware the only experimental evidence bearing directly upon the point is furnished by a series of experiments recently reported by Foster and Hawk. The subjects of the investigation were two young men. The study was divided into four periods, as follows, each period being seven days in length: (1) normal, (2) bolting, (3) Fletcherizing, (4) normal. A uniform diet was fed each subject throughout the course of the test. Meat contributed the major part of the nitrogenous portion of the diet. During the preliminary period of the experiment the food was masticated *normally*, in the next period the food was "bolted," in the third period it was Fletcherized, and in the final period normal mastication was again practised. The percentage utilization values when corrected for "metabolic products" were as follows:

Period.	Utilization, per cent.	
	F.	J.
Normal	97.0	95.5
Bolting	95.4	95.7
Fletcherizing	97.2	97.5
Normal	97.0	97.5

From the above data the authors conclude as follows: "Our data indicate that when meat is bolted in fifteen-millimeter cubes it is somewhat less efficiently utilized than when normally masticated or Fletcherized. However, the difference in utilization is not pronounced and cannot be considered as furnishing an experimental basis for the belief that food bolting is harmful to the organism. The protein portion of the diet was no more efficiently utilized when the food was chewed until carried down the œsophagus by the "swallowing impulse" than when it was masticated in a normal manner. In other words our data fail to show the advantages of Fletcherism or the harmfulness of food bolting." The final statement is not meant to convey approval of food bolting under all conditions. The bolting of food by persons possessing a derangement of any of the digestive, secretory or absorptive functions of the gastro-intestinal tract is another proposition. No data are available as to the actual utilization of ingested protein under such conditions.

Certain experiments of Conheim are of interest in connection with the above findings. This investigator equipped two dogs with duodenal fistulas, then fed the animals *finely hashed meat* and *meat cubes* respectively. It was found that the finely divided material left the stomach in one hour and thirty-five minutes, whereas the cubes remained two hours and thirty-one minutes. However only 59 per cent. of the finely hashed meat was digested in the stomach while 92 per cent. of the meat in the form of cubes underwent peptonization. It follows that although the

meat cubes remained longer in the stomach, more of the material was digested as a result. The passage of finely divided material into the stomach places the bulk of the digestive burden *upon the intestine*. In case coarse food is ingested the stomach assumes the digestive burden.

Inasmuch as we are told that the main function of the stomach is not a digestive one, whereas the intestine is the principal digestive organ, it would seem that any dietary procedure which will relieve the over-worked intestine and at the same time entail no loss of energy to the body is apparently worthy of consideration. These observations of Conheim may be taken in a way as evidence favorable to undermastication since we may conclude that any dietary procedure which will induce the stomach to assume offices commonly performed by the intestine is of advantage and tends to increased nutritional efficiency.

Non-protein Nitrogen in Metabolism. — All animal organisms need nitrogen in order that they may function normally. Until comparatively recently it had been considered that the essential nitrogen *must* be fed in the form of protein material, as non-protein nitrogen was believed to be nutritionally inefficient. In the intestine the ingested protein is reduced to amino-acids as the ultimate cleavage products and a certain quota at least of these acids are passed into the circulation and carried to the various tissues where they are utilized (Folin, Van Slyke and others). It is not surprising, therefore, that experiments made by Loewi, Henriques and Hansen, Abderhalden and associates, and others have indicated that satisfactory results may be obtained by the substitution of these amino-acids for the protein nitrogen of the diet.

That plants may go even further than the above and may synthesize protein from ammonium salts and other sources is well established. It was not believed that the animal organism possessed the power of forming body protein from non-nitrogenous sources other than the amino-acids above mentioned. Recent experiments make it evident that our ideas on this point must be revised. Many experiments show that a certain percentage of non-protein nitrogen in the form of ammonium salts may be utilized by the animal organism. It was first believed in order to demonstrate a nitrogen retention when nitrogen in the form of ammonium salts constituted the main bulk of the ingested nitrogen, that it was necessary that the diet should be one containing an abundance of carbohydrate. The nitrogen could then be conceived as forming an amino-acid complex with the carbohydrate and protein synthesis could follow (Grafe and Schlöpfer). Later Abderhalden denied the possibility of such an indirect synthesis. He says that there is no basis for the assumption that the animal body has the power of producing from carbohydrates the varied complexes which are essential for the construction of amino-acids or that such complexes if produced could be aminized by means of the nitrogen of the administered ammonia. Abderhalden in his recent discussions is inclined to consider the nitrogen retention as only *temporary* and that subsequent compensation occurs.

Contrary to the findings of Grafe and Schlöpfer it has been shown by Taylor and Ringer that it is not necessary to have carbohydrate in the diet in order to obtain retention of nitrogen from ammonium salts.

The data from an experiment by Taylor and Ringer in which a man was placed on a nitrogen-free diet for five days and on the sixth and seventh days received doses of ammonium carbonate, are of particular interest. Analyses indicated that about two-thirds of the ammonia nitrogen had been retained. They believe that the ammonia nitrogen is retained because of "a reversed reaction that leads to combination with the α -ketonic or α -hydroxy acids to form amino-acids which may be used in the upbuilding or sparing of body protein."

In the experiments of Grafe and Schläpfer nitrogen retention was obtained with both *inorganic* and *organic* salts of ammonium. Very recently Underhill and Goldschmidt have demonstrated that "Ammonium chloride shows an entirely different behavior from organic ammonium salts ingested by dogs maintained upon a high caloric non-nitrogenous diet. Ammonium chloride . . . fails to diminish the loss of nitrogen from the body . . . ; in other words nitrogen was not retained in the sense of Grafe and Schläpfer. It may, therefore, be concluded that ammonium chloride . . . is incapable of acting as a source of nitrogen supply for the nutritional needs of the body." According to these authors, the salt had a "marked toxic action" and that its ingestion may be "a distinct detriment to nutritive rhythm." They report that the ingestion of ammonium acetate or ammonium citrate was accompanied by a "considerable daily retention of nitrogen which failed to reappear during the after-period."

Autolysis and Intracellular Enzymes.—The recognition of the importance of enzymatic processes, and the increasing acquaintance with types of enzymes capable of transacting the work of the cells under physiological conditions, have directed attention to the possible significance of these enzymes in pathological processes. As certain functional activities have long been associated with definite morphological structures, the integrity of which was conceived to be essential for their work, pathology has depended upon structural or vague "functional" alterations to account for the unusual or abnormal. But since proteolysis, lipolysis, glycolysis, oxidation, deamination, are all referable to appropriate enzymes, some of which seem to be regulated by corresponding anti-enzymes or activated by kinases, new features are introduced into the study of pathological manifestations. In a system of coöperating and interdependent chemical reactions, it is quiet conceivable that the impairment or omission of one link in the chain may throw the entire complex out of gear. The autolysis of certain tissues in disease is doubtless associated with some such disturbance. Autolytic enzymes are widely distributed; and in phosphorus poisoning and acute yellow atrophy an intravital autolysis of the liver frequently leads to a softening of that organ, with formation of typical products of proteolysis. In carcinoma, in the lungs during pneumonia, in abscess formation, and especially where a destruction of polynuclear leukocytes is accompanied by a liberation of autolytic-enzymes, autolytic changes may take place. The proteolytic products are then further destroyed in the usual way or they may accumulate in the blood and be excreted as such. Autolysis seems to be the effective agent in the destruction or metabolism of all

necrotic tissues. The occurrence of increased quantities of amino-acids, like leucin, tyrosin, and glycocoll in the urine, is perhaps attributable in some cases to undue autolysis which is checked in conditions of health. It is not unlikely that analogous changes take place in the degeneration of nervous tissue, by which cholin is liberated from lecithins. As further peculiar products of tissue self-digestion, bactericidal and antitoxic products may be mentioned, and the lack of suitable glycolytic enzymes has even been proclaimed as a possible cause of the imperfect utilization of sugars in diabetes.

Acidosis.—This term is used to designate a pathological condition in which acids arise in metabolism. It is not easy to determine in every case whether the acid owes its origin to abnormal formation, or to imperfect destruction of some compound ordinarily generated in intermediary metabolism and at once subjected to further decomposition. There are several ways in which these acid products may become a source of harm. They are likely to withdraw from the body bases in combination with which they are then eliminated as relatively harmless salts; and when the organism is overwhelmed with large quantities of these unneutralized organic acids, toxic symptoms may be occasioned. The most interesting feature of the general condition of acidosis, whatever the mode of its generation, is the accompanying increased elimination of ammonia. This, however, does not necessarily signify any increased production of ammonia in metabolism. Ammonia is the acid indicator of intermediary metabolism. When mineral acids are introduced into the body, or organic acids are formed by some unusual circumstance within it, they are at once neutralized by ammonia, the nitrogen elimination in other types of compounds being correspondingly diminished. The dangers of acid intoxication are thereby avoided, and the alkali content of the blood and tissues protected from loss. This typical behavior of ammonia in intermediary nitrogen exchange is a valuable protective reaction for the organism; and, conversely, the elimination of proportionately large quantities of nitrogen, in the form of ammonium salts, is to be referred, not to any increased katabolism resulting in ammonia production, but rather to acids which have neutralized it prior to its conversion into urea. Of possible conditions which might imitate such an excretion there are many. The intermediary production of lactic acid, β -hydroxybutyric acid, aceto-acetic acid, glycuronic acid, oxalic acid, etc., suggests the types of acid compounds which may be formed. Mineral acids (phosphoric and sulphuric) may likewise arise in metabolism. As a rule the quantity of these is far too small to account for the high ammonia output in many pathological conditions, and it is necessary to assume the production of a considerable portion of *organic* acids. There are even cases in which the production of acids is sufficiently large apparently to call for a destruction of protein in order to furnish sufficient ammonia for the acidosis presented.

When the quantities of the chief bases, sodium, potassium, calcium, magnesium, and ammonium, and the chief acids, sulphuric, phosphoric, hydrochloric, and uric, eliminated in the urine, are compared or "balanced," any excess of the sum of the bases over the equivalent sum of

the acids may at once be referred to the presence of unknown organic acids. In the more extreme cases, other bases, calcium, magnesium, even potassium and sodium, may contribute to the "detoxicating" or neutralizing process, and the body may be robbed of its bases in addition to losses of protein katabolized to yield ammonia. The lethal symptoms in diabetic coma are those of an acid intoxication, while loss of alkali doubtless plays a contributory rôle in the effects produced.

The complications of perverted intermediary metabolism are far-reaching. The situation in diabetes is, perhaps, somewhat extreme, yet sufficiently characteristic to portray the salient features of acidosis. It is well, perhaps, to emphasize the fact that the fundamental disturbance is a nutritive one. Organic acids left unburned deplete the store of available bases. They may unite with ammonia, which the organism can almost always furnish with liberality when the protein of the diet is present in customary abundance, or which it can requisition by increased katabolism if need be. Or the acids may unite with other bases and induce a new series of nutritive difficulties; so that there are cases in which the extent of ammonia output is not a reliable measure of the degree of acidosis. In such instances the "balance" of acids and bases must be depended on for more reliable indications.

There are various forms of *hepatic* disease accompanied and even characterized by the chemical symptoms of acidosis. Cirrhosis, degeneration following phosphorus poisoning, acute yellow atrophy, and chronic abnormality of the liver, differing in their pathogenesis, are all characterized by relatively high proportions of ammonia-nitrogen in the urine. The characteristic high ammonia elimination in liver affections may be associated with an inhibition of the urea-forming powers of the hepatic cells. Seldom is urea absent from the urine, however, and the low urea output may equally well be attributed to the small protein intake of patients suffering from serious hepatic impairment. Furthermore, it has been found that even in advanced stages of hepatic degeneration ammonia salts administered by mouth can still be converted to urea. This may be due in part to the fact that urea is formed elsewhere than in the liver.

In many cases of acidosis the factor appears to be lactic acid. Much of the lactic acid doubtless is referable to carbohydrates; some of it may be derived indirectly from proteins. Perfusion of the glycogen-yielding livers of well-nourished animals with blood results in a production of lactic acid—a result not noted when glycogen-free livers from starving animals are used. But alanin, a protein derivative, likewise appears to form lactic acid under similar conditions. The relation between these compounds is very close. Contrasting these facts with the presumable origin of the pathological organic acids of diabetic urine from fats, it appears likely that acidosis as a condition can be brought about through imperfect intermediary metabolism of all the types of foodstuffs—fats, carbohydrates, and proteins.

An interesting disturbance of metabolism closely related to the phenomena of typical acidosis has been disclosed in connection with imperfect fat absorption from the intestine. When this is brought about by

lack of bile secretion or pancreatic disease, the fatty acids liberated in the alimentary tract from ingested fats appear to be excreted in the feces in increased quantity as soaps of calcium and magnesium. The diversion of these alkali earths into this channel of elimination occasions diminished excretion of them in the urine. Indirectly, the formation of lime soaps leads to a deficiency of alkali and a compensatory elimination of ammonia—phenomena characteristic of acidosis in metabolism. It has been suggested that the high ammonia output of infants suffering from gastro-intestinal disturbances may be directly attributable to disturbed absorption of fat with the chain of consequences just outlined.

Obesity.—It is difficult to say to what extent, if at all, corpulence represents a pathological condition; at any rate from a metabolic point of view the body is concerned here simply with an exaggeration of normal processes. When once a beginning has been made, the conditions thereby developed tend to perpetuate and aggravate the difficulties encountered. As the corpulence increases the muscles tend to be brought less into use, and the lack of exercise in turn tends to weaken them and render them still more unfit for work. The conservation of body warmth by the highly developed panniculus, the low metabolism of energy called forth by the attendant slothfulness, in addition to the abundant food intake in the corpulent, all contribute to protect the body fat. Alcohol plays a contributory part by affording a readily combustible compound which may speedily experience oxidation and protect the body-fat; and further, its action is such as to contribute to the general indifference and inactivity characteristic of obesity. The common observation of absence of any tendency toward corpulence in many individuals who eat very heartily and cultivate no unusual degree of muscular exertion leads one to ask whether the obese transform the potential energy of their foods more advantageously, or are subject to functionally diminished oxidative powers. Experiments have demonstrated conclusively that this is not the case. The oxygen consumption and carbon dioxide production of corpulent subjects are precisely comparable with that of non-corpulent individuals of the same weight.

Malnutrition and Related Conditions.—Ordinarily the disturbances noted are referable to variations in the quantitative relations of nutrition. As soon as qualitative changes arise the term *malnutrition* is more appropriately applied to the distinctly morbid states, and here the phenomena of autolysis, acidosis, protoplasmic disintegration and retarded katabolism of specific molecular complexes are met with. As regards the relation of fever to metabolism, the etiological and clinical conditions are too diverse to permit any general theory. Fevers are usually accompanied by a noteworthy increase in protein katabolism which contributes not a little to the serious physical impairment so often brought about. Undoubtedly it is quite correct to attribute this to a sort of involuntary inanition, but we believe that this alone is insufficient to account for all the disturbances of metabolism associated with fevers. Toxic products of bacterial or bodily origin undoubtedly may exert a direct action on tissue katabolism. In so-called “aseptic” fevers

the glycogen-content of the body appears to determine in no small measure the possibility of the rise in temperature. That the processes of intermediary metabolism may suffer qualitative disturbances is suggested by experiments like those of Mandel on the purin bases in aseptic fevers. A pronounced coincidence between the temperature and the purin bases has been observed; the quantity of uric acid eliminated varies with the purin bases; that is, the latter increase in amount as the quantity of uric acid diminishes, and *vice versa*. It is therefore not unlikely that a distinct relation between the fever and the appearance of certain products of incomplete cell oxidation, as shown by the excretion of purin bases, exists. The supposition that these bodies are directly concerned in the production of fevers is strengthened by the fact that the administration of xanthin and caffeine produces a decided rise in body temperature in otherwise healthy individuals. Without attributing to the purin bases the sole cause of the febrile temperature in the "aseptic" cases, it may be safe to assume that if other substances are concerned they are of similar origin and nature, *i. e.*, intermediary products of metabolism, the source of which is to be looked for in the circulating leukocytes and tissue cells.

A further specific factor is the continued new formation and simultaneous destruction of cells in inflamed areas. Where exudates are formed in considerable quantity an unusual addition may be made to the "circulating" protein of the body; in such cases the body metabolizes the excess of protein just as when an excess of the latter is furnished in the form of food. To what degree the disturbed thermogenic functions influence katabolism in fever is not determined beyond dispute. A retention of chlorides accompanying the increased protein decomposition occurs in many infectious diseases, like pneumonia and typhoid, which are attended with fever. A marked acidosis, especially intense in infancy, frequently adds to the complications which metabolism experiences in fever.

Indicanuria can scarcely be spoken of as a disturbance of intermediary metabolism, inasmuch as the primary cause usually lies in the preliminary putrefactive decomposition which the foodstuffs undergo before leaving the alimentary tract. The products of putrefaction, indol, skatol, phenol, and cresol, are synthesized in the liver to ethereal sulphates or glycuronates. The question as to whether the indol derivative indican cannot also arise in intermediary metabolism—in cases which are characterized by vigorous tissue decomposition, as in certain types of cachexia, in carcinoma of the stomach, etc.—has been actively discussed. We agree with Jaffé in concluding that the experimental evidence for a direct metabolic origin of indican is not convincing. At present no positive source of urinary indican is known outside of bacterial processes. The pathognomic significance of indicanuria (indoxyluria) is therefore restricted to the domain of those diseases which are attended with bacterial activity, either within or without the alimentary tract.

Preparation of Food.—The preparation of food plays by no means a negligible part in its subsequent fate in nutrition and may contribute both to its digestibility and its palatability. The appearance, flavor,

and odor, stimulate or modify the activity of the digestive glands through various channels, as has been shown by Pawlow and his pupils.

A variety of substances classed as "food accessories" exert an influence quite independent of any direct nutritive value. Some, like the extractive substances of meat, etc., are not entirely devoid of fuel value; others, like some of the inorganic salts, are indispensable, despite the fact that they convey no energy to the organism; while another class still, including ordinary condiments such as pepper, mustard, and other spices, exert an indirect influence on nutrition. The latter class includes substances which act directly upon sense organs exciting the sense of taste and thus inducing a reflex flow of the digestive secretions. In so far as they stimulate the appetite, they may create favorable conditions for incipient alimentary changes by the indirect effect upon the secretory glands concerned therein. Pawlow has said: "*Appetit ist Saft.*" The psychical effect of various factors in promoting, or—what is less familiarly recognized—in inhibiting indirectly the nutritive processes, is for the most part underestimated; for foodstuffs are not selected, in the ordinary course of events, with any due recognition of their real nutritive value, but rather in virtue of their palatability and the appeal which they make to the senses. Again, the group of substances represented by the extractives of meat as they are obtained in soups, etc., plays a part in stimulating the secretory glands. The question as to the effect of such substances upon the intermediate processes of metabolism has not yet received the consideration which it merits. Heretofore they have usually been studied from the standpoint of their pharmacological action. Yet taking alcohol as an illustration the more distinctly physiological aspects seem worthy of attention. Observations by Beebe have shown that it may noticeably alter the output of exogenous uric acid in man; and if other katabolic processes in the organism are similarly affected, the subsidiary changes induced in intermediary metabolism by such food accessories as alcohol may quite overshadow the influence which they exert in the preliminary digestive changes. Whether these subsidiary articles of diet, including meat extractives, tea, coffee, chocolate, alcohol, etc., are as necessary to us as the foodstuffs themselves is difficult to say. Common experience confirms their agreeable influence.

The inorganic salts, mineral nutrients or inorganic foodstuffs are essential owing to the fact that a lack of them must inevitably lead to physiological difficulties as a result of their continued loss in the excretions. The conservative efforts of the body are frequently displayed in the marked retention of some of these elements; for example, of chlorine in fevers. But unless restitution is made the defect inevitably manifests itself sooner or later. From the quantitative point of view the demand for chlorine and sodium (sodium chloride) is most conspicuous, and the search for this salt appears to be almost instinctive in both man and animals. The pathological symptoms which lack of some of these elements, such as iron and calcium, develops, is familiar. Occasionally the difficulty presented apparently involves a deficient absorption or retention of the compounds. We are inclined to believe that an increasing familiarity with the distribution of inorganic salts and their elements in

the natural foods will tend to lead to a substitution of *dietetic* methods of administration of these substances, in place of the therapeutic measures (artificial lime salts, iron salts, etc.) now employed so extensively. A radical change in diet will call for some consideration of the new adaptations of the inorganic foodstuffs accompanying it. Especially is this true for the growing organism. When the salts required by the latter are accurately known, a change from milk to some other form of diet may properly suggest the question whether the child will continue to obtain the necessary salts in sufficient quantities.

Composition of Foods in Their Relation to Nutrition.—Broadly speaking, it is customary to refer to the nutritive value of the various foods in daily use on the basis of their general composition; that is to say, the content of nitrogen or protein ($N \times 6.25$), fats (ether extract), non-nitrogenous constituents (digestible carbohydrates and insoluble cellulose), inorganic components and their heat of combustion. In discussing protein metabolism it has been pointed out that the nitrogenous compounds are by no means equivalent or identical in their physiological rôle, and the peculiar position of the purin-containing foods was emphasized. The great divergence in the distribution of purin derivatives is made manifest in the figures compiled by Walker Hall, as shown in the following table.

PURIN CONTENT OF COMMON FOODS

Food.	Average percentage of purin nitrogen.	Purin bodies (grams per kilo).
Fish:		
Cod023	0.582
Plaice032	0.795
Halibut041	1.020
Salmon046	1.165
Meats:		
Tripe023	.582
Mutton038	.965
Veal046	1.162
Pork048	1.212
Beef, ribs045	1.137
Beefsteak083	2.066
Liver110	2.752
Sweetbread402	10.063
Chicken051	1.295
Cereals:		
Bread, white	none	
Rice	none	
Oatmeal021	.530
Vegetables:		
Pea meal015	.390
Beans025	.637
Potatoes	trace	trace
Onions003	.090
Cabbage	none	
Lettuce	none	
Asparagus009	.215
Beers005	.125
Wines	none	
Milk	minute trace	minute trace

From this summary it is easy to arrange a dietary practically free from purin-containing foods and yet adapted to physiological require-

ments. For this diet cereals, milk, butter, eggs, certain green vegetables, sugars, etc., form the basis; and the output of urinary purins soon falls to the endogenous level thereon. In illustration of this we quote from Rockwood a diet experiment in which two subjects subsisted for nearly two weeks on a ration consisting of milk, 1350 cc.; prepared cereal, 35 grams; sugar, 20 grams; crackers, 250 grams; cheese, 30 grams; eggs, 96 grams; apples, 90 grams; wheat bread, 50 grams; butter, 15 grams; confectionery, 100 grams; during this period the average daily outputs of nitrogen and uric acid in the urine were respectively:

	A.	B.
Nitrogen	11.580 grams	11.390 grams
Uric acid305 grams	.340 grams

The widespread use of cereal preparations makes it worth while to consider briefly to what extent some of the claims have justification. A comparison of animal foods with those of vegetable origin as sources of protein and energy is afforded by the following figures (Milner):

	Protein, per cent.	Energy per gram, calories (large).
Oat preparations	16.1	4.423
Wheat preparations	21.1	4.032
Corn preparations	8.6	3.894
Rice preparations	8.3	3.907
Beef, lean round	19.5	1.795
Beef, fat round	16.1	3.104
Bread, white	9.2	2.885
Bread, graham	8.9	2.872
Cheese, full cream	25.9	4.674
Potatoes	2.2	0.892

Milner has summarized the essential features with respect to modern cereal preparations, especially the ready-to-eat products, "breakfast foods," etc., in these words: "The composition of the different products depends upon that of the grain from which they are made, and the extent to which the bran and germ have been removed in the manufacture. In general, the prepared product from any grain has much the same composition as that of flour or meal from the same grain. Different brands of similar nature when made from the same grain do not differ in average composition any more widely than different lots of the same brand. . . . The differences in actual nutritive value of the products from the same grain are therefore on the average so small that they may be disregarded in choosing between them. However, the oat preparations contain noticeably larger proportions of nutrients and energy than those of other grains, and as they are when properly cooked no less thoroughly digested the actual nutritive value of the oat preparations appears to be greater than that of the preparations from other grains.

"The nutritive value of the 'malted' or so-called 'predigested' preparations is no greater than that of other preparations from the same grains. In some instances the attempts to convert insoluble starch into more soluble material by the use of malt have been to a small degree successful, and to that extent the preparations have been rendered

more easily digestible; but just as much and even more is accomplished by thorough cooking. In most of the malted preparations the quantity of starch actually converted is, however, very small and in some cases none has been changed.

Vegetarian or Non-meat Diets.—Most familiar is vegetarianism, a system of living which teaches that the food of man should be derived directly from the plant world. In view of the widespread advocacy of this regime, it may be worth while to consider its physiological aspects. At the outset, it should be noted that a diversity of views has entered into the so-called vegetarian doctrines. The most radical reformers have abstained not alone from all food of animal origin but also from tubers and underground roots, eating only vegetables and fruits grown in the sunlight; others again reject cereals and live on fruits, nuts, and milk; while the most conservative exclude only fish, flesh, and fowl from their diet. The latter form of diet is termed the "non-meat" or "meat-free" diet.

Among the more strictly scientific arguments advanced against the use of animal foods are those relating to the dangers of disease lurking in them. This applies chiefly to the flesh of animals; such foods as eggs, milk, and butter, all derived from animals, are not ordinarily excluded from the modern vegetarian dietary, but rather contribute thereto in considerable measure. The high content of "extractive" substances—creatin, purin bodies, inorganic salts—in meat is referred to as an undesirable feature. These fail in part to yield any energy to the organism, and again becoming partially oxidized to compounds like uric acid, they may have a significance in certain pathological conditions. On the basis of the facts now available, no serious objections against the small quantities of the meat bases daily ingested in an average dietary can be formulated for the healthy individual. Apparently they belong to the same category as many other food accessories, such as tea, coffee, and alcohol, and are open to similar criticism. Certain experiments by Thompson, Caldwell, and Wallace indicate that increased body weight, retention of nitrogen, and a decrease in the nitrogen lost in the feces follow the addition of meat extracts to the diet. In older experiments the supposed influence of meat extract in increasing the nutritive value of vegetable foods was not substantiated. However, experiments recently reported by Wolff indicate that the addition of meat extractives to a vegetable diet improved the availability of fat and starch. From the clinical standpoint it has been quite definitely established that the withdrawal of meat from the dietary of cases of hyperacidity has been followed by most satisfactory results.

We are inclined to believe that rational objections against a meat diet are applicable with respect to quantitative aspects rather than to the chemical make-up of such dietaries. In other words, it is the abuse of meat in modern dietaries which should be charged with any dangers attaching to the employment of this animal food; and the disadvantages of an excessive protein diet apply with far less force to vegetarian regimes, owing to the proportionate nitrogen deficiency of the ordinary foods included in them.

An argument in support of the vegetarian diet is based upon the supposed structural adaptation of the alimentary canal to such a regime. In reply it may be pointed out that a mixed diet is admirably utilized in man in the light of experimental evidence. There are no convincing physiological or anatomical grounds for recommending an *exclusive* diet of either animal or vegetable origin. The disadvantage attaching to the exclusive use of foodstuffs offering a large content of indigestible and unutilizable residues in the gastro-intestinal tract has frequently been urged against the vegetarian. Fruits and vegetables are extremely bulky in proportion to the available nutrients in them, and may entail considerable alimentary waste. In fairness, a sharp distinction must be drawn between vegetable diet and vegetarian diet.

If we attempt to separate fact from fancy in an estimate of the nutritive significance and possibilities of vegetarian diet, there can be no question regarding the actual *possibility* of sustaining life with foods drawn exclusively from plant sources. Careful studies of the metabolism of individuals living largely or entirely on such dietaries are available in sufficient numbers to demonstrate with scientific accuracy what familiar observations have long indicated. Nor can there be any question as to the possibility of sustained and vigorous muscular exertion by person accustomed to a vegetarian regime. In fact experiments on record indicate that individuals subsisting on a restricted vegetarian diet have more strength and endurance than those including meat in their dietary. This is perhaps no more than might be expected, since it has been demonstrated that the essential source of energy liberated in muscular work is to be found in non-nitrogenous foods, the preponderance of which specially characterizes the vegetarian diet. There is, however, no evidence that the vegetarian utilizes his food better than the meat eater. However, where advantage accrues is in the moderation in diet which the so-called vegetarian regime tends to encourage. The appetite is stimulated to a lesser degree than by meats and meat products, and this in conjunction with the usual more bulky character of vegetable foods diminishes greatly the tendency toward overeating. The practice of temperance in matters of diet may be facilitated by the introduction of vegetarian methods, thus contributing therapeutic possibilities applicable in the treatment of metabolic disorders related to overnutrition or similar perversions—gout, plethora, obesity, etc. There are idiosyncrasies in which vegetable as well as animal foods meet with difficulties in the way of practical use. One is inclined to emphasize the desirability of using common-sense in the application of dietetic rules, remembering that man is well adapted by nature and experience to subsist on a variety of foods. Vegetarianism may have its virtues, as too great indulgence in flesh foods may have its serious side; but there would seem to be no sound physiological reason for the complete exclusion by normal persons of any one class of foodstuffs under ordinary conditions of life.

Certain experiments (Slonaker) may be taken as evidence against vegetarianism. Rats served as subjects and the experiments demonstrated that the rats which were fed a *mixed* diet were much more active

and voluntarily did more work (rotary cage) than the vegetarian rats, the actual ratio being $7\frac{1}{2}$ to 1. The investigator placed four rats, of same parentage and age, in rotary cages with speedometers attached. During an interval of twenty-five months the four rats had travelled the following distances: Meat-eating female rat, 5477 miles; meat-eating male rat, 1447 miles; vegetarian female rat, 447 miles; vegetarian male rat, 200 miles. Slonaker reports that the vegetarian rats became old earlier than those which ate meat and moreover that they were frail, weak, and without energy. He found the average life of the meat-eaters to be one thousand and twenty days, whereas that of the vegetarians was five hundred and five-five days.

It is difficult to determine just how far we may apply these striking results to man. It is true that the rat, like man, is by nature an omnivorous animal. Moreover it has recently been shown (Folin and Morris) that "the percentage composition of rat urine differs but little from that of human urine." This animal is also being used in very important nutrition experiments (Osborne and Mendel), which are believed to have a direct application to human nutrition.

The possibility of "universal vegetarianism" has been considered by Taylor. If this system of diet were carried out consistently the human race would of necessity forego the use of leather and fur. Taylor says: "Unhesitatingly it may be stated that the area of the earth's surface now under cultivation could not, with the present methods of agriculture, dependably produce enough plant albumin to meet the needs of the present population. . . . To meet these needs with plant albumin and dairy products the world's production of grains and legumins would need to be doubled at the least. It is quite certain that this could not, with the uttermost efforts of the world's population, be dependably accomplished at present. . . . The difficulties would not be technical, but human. To accomplish them the present intelligence of the human race, the dependable intelligence of the working race of mankind, would be wholly insufficient; the race has not attained to-day the scientific stature necessary to reach and pluck these fruits of knowledge. For the present, therefore, it is certain and beyond speculation that to place the human race on the basis of ethical vegetarianism would be to expose the race to the mercy of Nature, just as the vegetarian population of India is yearly at the mercy of the yield of grain."

The field of nutrition is one of immense importance to the physician. If we examine into the recent advances in medicine we will find that a large percentage of these have been made possible by the aid of a knowledge of physiological chemistry and nutrition. I believe with Osler that "The future of medicine rests with clinical chemistry and nutrition."

CHAPTER XVII

DIABETES MELLITUS AND INSIPIDUS

By THOMAS B. FUTCHER, M.B.

DIABETES MELLITUS

Definition.—A disorder of carbohydrate metabolism characterized usually by progressive loss in weight, thirst, and polyuria, and by the persistent excretion of glucose in the urine while the individual is on a diet containing only moderate amounts of carbohydrates, or, in certain instances, even when no carbohydrates are ingested. Fat and protein metabolism become secondarily affected during the course of the disease. Diabetes is not an entity but must be considered more as a symptom-complex dependent upon a great variety of causes.

Etiology.—A study of the *incidence* of the disease would seem to indicate that it was on the increase in the United States. The United States census for 1850 gave 0.9; for 1860, 1.2; for 1870, 2.1; for 1880, 2.8; for 1890, 5.5; for 1900, 9.3; and for 1910, 14.9 deaths from diabetes per 100,000 population. In the census year of 1910 there were 8805 deaths from the disease in the United States. In this year the ratio of deaths from diabetes to the total number of deaths was 1 to 104. In Baltimore, the death-rate from the disease in 1900 was 8.3, and in 1910, 14.8 per 100,000 population. The incidence of diabetes in Baltimore is further indicated by the fact that in the twenty-four years since the opening of the Johns Hopkins Hospital, ending May 15, 1913, there were 335 cases under treatment in the medical wards out of a total of 30,871 medical patients. Statistics indicate that the disease occurs with about equal frequency in the United States and European countries.

Race.—The disease appears to be about twice as common in the white as in the colored race. In the Johns Hopkins Hospital series of 335 cases there were 36 in negroes, or 10.7 per cent., giving a ratio of 8 to 1. The ratio of white to colored admissions in the medical wards during this period has been about 4 to 1. Expressed in terms of susceptibility, it would appear then that in Baltimore the white population is only twice more liable to the disease than the colored. The United States census report for 1900, on the other hand, gave only 48 deaths from the disease in the colored race out of a total of 4672 deaths from diabetes. Of these 28 were in males and 20 in females. All authorities agree that the Hebrew race is particularly susceptible. Frerichs states that of his 400 cases, 102 were Jews. Wallach clearly demonstrated its greater frequency among the Hebrews of Frankfurt. From 1872 to 1890 there were 171 deaths from diabetes in that city. The proportion

(674)

of deaths from diabetes to the deaths from all causes was six times greater among the Jews than among the rest of the inhabitants. The factors occasioning this greater susceptibility in Hebrews are not well understood. It has been variously ascribed to greater instability of the nervous system, fondness for sweets, and overeating and sedentary habits particularly among the better classes. Diabetes is very common among the educated and commercial classes in India, and Rose and Sen have shown that it is the Hindoos who chiefly suffer. The disease is said to be very uncommon in China and Japan.

Heredity, undoubtedly, is a factor in many cases. Several brothers and sisters may be affected. While one or other parent may have the disease, they often escape, and an uncle, aunt, or cousin may suffer from it. Richard Morton, who termed the disease *hydrops ad matulam*, or dropsy of the chamber-pot (Phthisiologia, 1689), records a family in which four children were affected, one of whom recovered on a milk diet and diascordium. Pleasants found only 6 cases, or 5.3 per cent., with a family history of diabetes, in the first 112 diabetics in Osler's clinic at the Johns Hopkins Hospital, and reported a family in which two brothers, two sisters, an uncle, and a grand-uncle had the disease. Of particular value is the series reported by Fitz and Joslin in which especial inquiry was made and in which heredity was found to play a rôle in 23.8 per cent. Naunyn obtained a family history of diabetes in 35 out of 201 private cases and in only 7 of 157 hospital cases. Obesity is often a feature in these hereditary cases.

The possibility of one person contracting the disease from another by *infection* was first suggested by Schmidt in 1890. Among 2320 cases, he recorded 26 instances in which the disease appeared in apparently healthy persons, living in intimate association with diabetics. These were chiefly married females who contracted diabetes after nursing husbands suffering from the disease. These are cases of so-called "conjugal diabetes." Oppler and Külz, in 1896, reported 47 married couples among 3489 diabetic patients or 1 to 93.3, or 1.08 per cent. Senator, in the same year, stated that among 770 of his cases of diabetes, there were 9 instances, or 1.19 per cent., in which a man and wife suffered from the disease. For several years the writer had a husband and wife, both diabetic, under his care. The wife was shown to be diabetic in 1899, and sugar was first detected in the husband's urine in 1902. Both patients were rather obese. When one eliminates the influence of heredity, worry, obesity, and dietetic conditions in these cases, little evidence remains to support the hypothesis that diabetes can actually be contracted by one individual from another.

No *age* is exempt from the disease, but most authors agree that the largest number of cases occur in the sixth decade, that is, between fifty and sixty years of age.

The incidence as to decades in the Johns Hopkins Hospital series of 335 cases is shown in the following analysis:

1 to 10	11 to 20	21 to 30	31 to 40	41 to 50	51 to 60	61 to 70	71 to 80
8	25	44	61	69	89	33	6

It will be seen that the largest number of cases, 89 or 26.5 per cent., occurred in the sixth decade. These figures agree closely with those of Frerichs, Seegen, and Pavy, all of whom found the largest number of cases in the sixth decade, their percentages being 26, 30, and 30.7 respectively. Wegeli, in an analysis of 102 cases in children under sixteen years, found the age distribution to be as follows: under one year, 3; one to five years, 26; five to ten years, 31; ten to sixteen years, 42. Stern mentions a case in which a child was apparently born with glycosuria, and in which recovery took place in eight months. Knox has collected from the literature 16 cases in infants under one year of age.

Diabetes is decidedly more common in the *male* sex. In our series of 335 cases there were 214 males and 121 females. Of the 4672 deaths from the disease in the United States in 1900, 2650 were in males and 2022 in females. This disproportion is not so marked in childhood and extreme old age, when the figures are more nearly equal. In the Johns Hopkins Hospital, of the 36 cases in negroes, 20 were in females and 16 in males.

In spite of the fact that the disease is often seen in its severest form among the poorer classes, it is undoubtedly more common in those of good *social position*. Not infrequently the onset of the disease is preceded by a history of fright, severe nervous strain, mental worry, and irritation.

Obesity plays a very important rôle. Diabetes occurs very frequently in persons who become very stout during middle life. Frerichs had 59 cases of obesity among 400 diabetic patients, or 15 per cent. It occurred in 30 per cent. of Seegen's and in 45 per cent. of Bouchard's cases. Women are liable to become stout at the climacteric period, and are particularly prone to become diabetic at this time. Diabetes occurring in fat individuals is termed "lipogenous diabetes." When diabetes occurs in obese persons of middle age it is usually of a mild type, and the prognosis is more favorable, the glycosuria disappearing on a rigid diet. The obesity usually precedes the glycosuria by several years. The fat diabetic is more commonly met with in private than in hospital practice. Occasionally obesity develops rapidly in young persons before the twentieth year. These subjects may also develop diabetes, which is always of a grave type and rapidly leads to a fatal termination.

Universally admitted as this connection between obesity and glycosuria is, the nature of the relationship between fat and carbohydrate exchange is not at all well understood. Von Noorden is of the opinion that the obesity is an early symptom of the diabetic condition, and that it develops long before glucose makes its appearance in the urine. Owing to the belief that the obesity is caused by the diabetic condition, he has given it the name "diabetogenous obesity." He believes that in every case of true diabetes not only the oxidation of carbohydrates, but also their conversion into fat is restricted. He says that it is conceivable that there are cases in which at first the power to burn up the sugar in the organism is alone interfered with, while the conversion of carbohydrates into fat still goes on. Under these circumstances the working or muscle cells of the body are richly bathed in a nutritive sugar solution; nevertheless they are starved because they cannot, or

at least can only with difficulty, seize upon the sugar molecule, owing to deficient powers of oxidation. As a consequence there occurs a sort of tissue-hunger, which excites reflexly a sharper appetite and leads to the ingestion of a greater quantity of food. The latter results directly in an increased deposit of fat. According to von Noorden, such persons are diabetic, only they do not excrete sugar externally through the urine, but into the easily accessible layer of adipose tissue.

We might suppose that the prolonged excessive use of *carbohydrate food* would favor the development of diabetes. There seems no satisfactory evidence favoring this view, however. Cantani stated that the majority of his Italian patients subsisted largely on farinaceous food. He believed the diet was an important etiological factor. In Ceylon, also, where diabetes is common, large quantities of saccharine food are taken. The Chinese, on the other hand, rarely suffer from diabetes, although their diet consists chiefly of carbohydrates.

The metabolic disturbances underlying *gout* seem to favor the occurrence of diabetes. Grube, of Neuenahr, found that 16 out of 177 diabetic patients suffered from gout, and 23 had gouty parents (hereditary alternating gout). This proportion is probably unduly high owing to the fact that the waters at Neuenahr are especially recommended for the mild cases of diabetes occurring in gouty patients. Von Noorden says that the connection between the two diseases may manifest itself in various ways. The patient may suffer from typical attacks of gout in middle life, and later the attacks cease and glycosuria appears. On the other hand, cases are observed in which attacks of gout alternate with glycosuria (diabetes alternans). In all these cases the diabetes is of a mild type and is compatible with a long life.

In occasional instances, diabetes may be traced to a *syphilitic infection*. These cases are undoubtedly rare. Feinberg reported 3 cases of diabetes and 1 of glycosuria which he attributed to a syphilitic infection. When syphilis plays a part, the lesion is most probably a local one, and most likely to be situated in the region of the medulla or pituitary gland. Nutritional changes in the brain and pancreas from syphilitic arterial disease must be considered as a possible cause.

In certain cases the diabetic symptoms have begun shortly after one of the *infectious diseases*. Cases have followed typhoid fever, scarlet fever, cholera, diphtheria, and rheumatic fever. There seems no satisfactory evidence supporting the view that malaria is a contributory cause. Williamson thought influenza played a part in 6 out of 100 cases in which special inquiry was made into the previous history.

In rare instances diabetes appears to be induced by *pregnancy*. The disease may manifest itself only during the pregnant period, being absent in the intervals. It is an occasional accompaniment of *Basedow's disease* but more often a transitory glycosuria occurs. Lowered tolerance to carbohydrates in this disease has been demonstrated by numerous observers. Falkenberg has reported cases in which glycosuria has followed extirpation of the thyroid. Marie, Fraenkel, Strumpell, and others, have observed it in *acromegaly*. Recent investigations of Cushing and others seem to indicate that a glycosuria probably occurs

in all cases of this disease during the stage of hyperpituitarism. A transitory glycosuria occasionally supervenes after attacks of *gall-stone colic*. It may occur after the administration of a general anesthetic, and in other forms of narcosis. Asphyxia, by carbon monoxide or carbon dioxide, may cause a glycosuria, or even a true diabetes.

Glycosuria in Lesions of the Central Nervous System.—Although isolated observations had previously called attention to an association between certain lesions of the nervous system, and glycosuria or diabetes, it was Claude Bernard, who in 1849 first demonstrated this relation by his celebrated “*piqûre*” experiment. He showed that by puncturing a point in the floor of the fourth ventricle, situated between the centres for the pneumogastric and auditory nerves, a hyperglycemia, polyuria, and a transitory glycosuria occurred, lasting six hours in the rabbit, and about forty-eight in the dog. Although this experiment has not been confirmed in man, it is not surprising that certain injuries to the central nervous system cause sugar to appear in the urine. Thus glycosuria or a true diabetes may follow severe *trauma*. Ebstein obtained a history of external injury in 6 out of 116, and Williamson in 6 out of 100 cases of diabetes. Ebstein collected 50 cases of traumatic diabetes from his own clinic and from the literature. In one-half of these, the head was the seat of the injury. Glycosuria is more liable to follow trauma in this situation. Injury to the pituitary or its stalk may account for the glycosuria. In other cases, injuries to the neck, liver, kidney region, and pubes have been followed by it. Ebstein thought that individual predisposition was a factor in determining the occurrence of diabetes in these cases. Glycosuria may also develop in the course of a traumatic neurosis. Before attributing glycosuria or diabetes to a traumatic neurosis it should be definitely demonstrated that glycosuria did not previously exist. In scarcely any of the reported cases has this been done. These cases occasionally are the subject of legal action.

Glycosuria or a true diabetes may occur in *organic lesions of the brain*, without Bernard's “*diabetic centre*” being necessarily involved. Glycosuria is not infrequent after *cerebral hemorrhage*. It rarely appears earlier than two hours after the apoplexy, and usually clears up within six days. Naunyn knows of only one instance where the glycosuria has passed over into a true diabetes—a case reported by Meyer. A true diabetes may be occasioned by a *tumor* of the pons, medulla, or cerebellum. Osler cites a case, seen with Reiss at the Friedrichshain, Berlin, of a woman with anomalous cerebral symptoms and diabetes, in whom at postmortem a *cysticercus* in the fourth ventricle was found. Ebstein reported 4 cases in which there was a coincident occurrence of *epilepsy* and diabetes, but attributes the two diseases to the same cause. Similar observations have been made by Naunyn, Jacobi, and Lallier. Naunyn observed a case in chronic *encephalomalacia*. Observers agree in the comparative frequency of glycosuria, or a mild diabetes, in *general paresis*. Bond reports having found it in 10 per cent., and Strauss in 9 per cent. of their cases. Glycosuria is an occasional accompaniment of *tabes dorsalis* and *multiple sclerosis*. Tumors of the vagus and involvement of the nerve secondary to a caseated lymph gland

have been associated with glycosuria. The latter is sometimes seen in severe cases of sciatica, but in this connection it must be remembered that neuralgias are not uncommon in diabetes. Isolated instances of disease of the abdominal *sympathetic ganglia* accompanied by glycosuria have been reported. Functional disturbances of the *autonomic nervous system* with its intimate relationship to the chromaffin system, including the adrenals, are now believed to be responsible for some cases of glycosuria.

Disturbances of the Internal Secretions.—The part played by the internal secretions is of prime importance in carbohydrate metabolism. The study of their functions in recent years has shed a great deal of light on the etiology of diabetes and further investigation will probably help to clear up many points still obscure.

(a) *The Pancreas.*—Since Thomas Cawley, in 1788, recorded a case of diabetes in which the pancreas was atrophied and contained calculi, changes in the gland have been from time to time reported in this disease. In 1877, Lancereaux, on the strength of numerous clinical observations, described a special form of diabetes under the name of *diabète pancréatique ou diabète maigre*, in which emaciation was the striking feature, in contradistinction to *diabète gras*, in which the subject remains well nourished, and in which the pancreas was not thought to be involved. A great advance in our knowledge of the relationship between the pancreatic functions and diabetes resulted from the publication by Minkowski and von Mering, in 1889, of the results obtained from the extirpation of the pancreas in animals. They demonstrated that complete extirpation of the pancreas in dogs and other animals was constantly followed by a fatal diabetes with all the classical symptoms including coma. It was found that when more than one-tenth of the gland was left intact diabetes did not occur. The ability of the liver and muscles to store glycogen was destroyed and only traces could be found in these organs after the administration of large quantities of carbohydrates. There is always a hyperglycemia, however, the amount of sugar in the circulating blood reaching as high as 0.5 per cent. within twenty-four hours. Minkowski and von Mering formulated the following hypotheses; either some substance which has an inhibitory action on sugar conversion collects in the blood after extirpation of the pancreas, or else, after this operation, some substance is wanting or function abolished which, under normal conditions, serves to facilitate the conversion of carbohydrates. Lépine, of Lyons, in 1892, was the first to advance the view that diabetes in man, and after extirpation of the pancreas in animals, is due to the failure of the pancreas to produce a "glycolytic ferment," which occurs as an internal secretion.

Diabetes and Organic Diseases of the Pancreas.—It is not surprising that pancreatic lesions in man are often followed by diabetes. Lesions of no other single organ so frequently give rise to the disease, and evidence is steadily accumulating that many cases of diabetes, apparently unaccompanied by any organic lesion, are actually due to pancreatic disease made out only on microscopic examination. Most of the published statistics, showing the percentage of cases of diabetes with involvement

of the pancreas, are altogether unreliable in the light of recent knowledge, owing to the fact that microscopic examinations were omitted in the majority of instances. According to Naunyn, a *pancreatic calculus* has been the most frequent lesion. Others would consider atrophy of the gland, *chronic interstitial pancreatitis*, the commonest pathological change. In the case of a calculus, it must be remembered that there is always an associated pancreatitis. Diabetes may occur when *cancer* involves the whole or greater part of the gland, but it is absent in many of these cases. Hanseemann, and Bard and Pic attribute the absence of the glycosuria to the assumption of the pancreatic function by the cancer cells. It is surprising that glycosuria does not occur oftener in *acute hemorrhagic pancreatitis* with complete destruction of the gland. Seitz collected 100 such cases, in not a single one of which did glycosuria occur. This may be accounted for by the early death in most of these cases. Benda and Stadelmann reported a case with glycosuria. Sugar in the urine occasionally occurs in patients with *pancreatic cysts*.

The Association between Diabetes and Lesions of the Islands of Langerhans.—The year 1900 marks a new epoch in our knowledge of the etiology of diabetes. In that year Opie published from Welch's laboratory a pathological study on interstitial pancreatitis in which he for the first time demonstrated a connection between disease of the islands of Langerhans and diabetes. His results were published more in detail in the following year. These groups of cells were first described by Langerhans in 1869. They are composed of columns of cells having no communication with the ducts of the gland, but being in intimate relation with a rich capillary net-work. They are about the size of a kidney glomerulus, measuring 0.2 mm. in diameter. The islands are situated for the most part in the centres of the ordinary gland acini, and are quite distinct, structurally and functionally, from them. They are distributed throughout the whole gland, but are more numerous in the tail than in the body or head. They are composed of small, irregular, polygonal cells having a round nucleus and homogeneous protoplasm.

Opie described two forms of chronic interstitial pancreatitis—an *interlobular* and an *interacinar* type. He found that certain of these cases, particularly of the interacinar type, suffered from diabetes. Histological examination of the pancreas in these cases showed extensive atrophy of the islands of Langerhans. These observations led him to make a systematic study of the pancreas in all cases of diabetes that came to autopsy. In a considerable percentage he found a hyaline degeneration of the island cells, those of the ordinary acini being uninvolved. Ssobolow, working independently, confirmed Opie's findings in 1901. W. G. MacCallum found that if a portion of the pancreas is separated from the rest of the gland and its duct tied it atrophies and leaves a tissue containing enlarged islands of Langerhans. If the remainder of the pancreas is removed this atrophied portion is able to ward off glycosuria, but if this is now removed glycosuria supervenes. Joslin and many other observers have confirmed Opie's work. All cases of glycosuria and diabetes do not show these changes in the islands, however. When a microscopic lesion is not demonstrable one must consider the

possibility of a functional disturbance of these islands, just as we can have a functional disturbance of the acid-producing cells of the gastric mucosa. Undoubtedly it is in these islands that the internal secretion that influences carbohydrate metabolism is produced, although this is difficult to demonstrate absolutely owing to their minute size and the impossibility of isolating them. According to Zuelzer and others the function of this secretion is to retard glycogenolysis in the liver. Otto Cohnheim believes that the internal secretion of the pancreas acts as an amboceptor to an enzyme produced in the muscles and that it is by the interaction of these two glycolytic bodies that the glucose of the blood is burnt up in the muscle tissue. The hormones of the pancreas and adrenals are believed to antagonize each other, the former retarding and the latter accelerating glycogenolysis.

At this point also must be mentioned the interesting group of cases of "bronze diabetes," occurring as a late manifestation of the remarkable affection known as *hemochromatosis*. The latter condition is characterized by a peculiar pigmentation of the skin and viscera, associated with a form of hypertrophic cirrhosis of the liver and extensive sclerotic changes in the pancreas, and accompanied in the late stages by a persistent glycosuria. Hanot and Chauffard first described these cases in 1882, and Hanot in 1886 suggested the name *diabète bronzé* for this type of diabetes, and, as he considered the liver changes secondary to the diabetic condition, he gave the name *cirrrose pigmentaire diabétique* to this form of cirrhosis. The true nature of the affection was first revealed in 1889 by von Recklinghausen, who described the disease under the name of hemochromatosis. He showed that the pigmentation of the skin and viscera is due to the deposition of an iron-containing pigment, hemosiderin, and a non-iron-containing pigment, hemofuscin.

According to the latest conception of the disease, hemochromatosis is to be considered as a primary affection of the blood in which the red cells are made more vulnerable, causing them to disintegrate more readily and to give up their hemoglobin. Sprunt in his study of the disease says that "it may be considered a metabolic disease implicating many of the body tissues, and, manifested, especially, by a change in the chromogenic groups of the proteid molecule with the deposition of pigments." The hemosiderin possesses a brown color and is deposited mainly in the cells of the liver, pancreas, lymphatic and sweat glands. The hemofuscin, on the other hand, is finer, of an ochre-yellow color, and is present in the smooth muscle fibres of the stomach, intestines, blood and lymph vessels, and occasionally in those of the urinary bladder, ureter, and vas deferens. Hess and Zurhelle have recently made very careful studies of two cases of "bronze diabetes," that is, two cases of hemochromatosis which had advanced to the diabetic stage. As a result of their studies they incline to the view that the cirrhosis of the liver and the formation and deposition of the pigment are dependent upon some common cause. They hold that some toxic substance, possibly alcohol, causes disturbances in metabolism which bring about the above changes. A lipemia, which was present in one of their cases, is explained in the same way. Their investigations also go to show

that a sharp distinction between hemosiderin and hemofuscin cannot be made. They claim to have found them side by side in the same cell with gradual transitions from one into the other. The hemoglobin of the blood is in all likelihood their common source. As a result of the local deposition of the pigment in the liver and pancreas, a chronic interstitial inflammation occurs, producing in the case of the liver, a hypertrophic pigmentary cirrhosis, and, in the case of the pancreas, an interstitial pancreatitis of a pigmentary type. In the early stages or early years of this affection sugar does not appear in the urine, and it is only when the changes in the pancreas become so advanced that presumably the islands of Langerhans are largely or completely destroyed that diabetes develops. Sprunt suggests that the diabetes may be referable to the diminished oxidation powers of the body due to the pronounced disturbance in the iron-containing constituents of the tissues, assuming these iron compounds to be catalytic agents in oxidizing processes. This theory was advanced owing to the fact that in some of his cases the islands of Langerhans were relatively unaffected. Whenever hemochromatosis, either with or without diabetes, is suspected, the correctness of the diagnosis *intra vitam* will be made much more probable by removal of portions of the pigmented skin and the finding of iron-containing pigment in the cells of the sweat glands by the potassium ferrocyanide test, and of the ochre-yellow hemofuscin in the muscle fibres of any bloodvessels that may be present.

Naumyn, Grube, Laache, and Fleiner have drawn attention to the frequency in the association between *arteriosclerosis* and diabetes. Nutritional changes in the pancreas, due to sclerosis of the pancreatic arteries, has been suggested as the assignable cause. Fleiner reported a case of diabetes in a patient with general arteriosclerosis in which there was a diffuse interstitial pancreatitis with marked thickening and obliteration of the branches of the pancreatic artery.

(b) *The Adrenals and Chromaffin System.*—The chromaffin system is composed of those cells in the body which have an affinity for chromic acid stains. These cells are contained, for the most part, in the adrenals. They are found accompanying the sympathetic nerves; they occur also in the retroperitoneum, and they are grouped together in the pelvis to form the so-called Zuckerkannd organ. All these cells apparently possess the same functions.

Clinically, we know of no organic disease of the adrenals that produces glycosuria or a true diabetes. Yet there is now abundant experimental proof that the adrenal hormone powerfully influences carbohydrate metabolism. F. Blum, in 1901, was the first to produce glycosuria in dogs by the intravenous injection of epinephrin. These results have been amply confirmed by Herter and many others. For a long time it was not known how this glycosuria was brought about. Through the work of Zuelzer, von Noorden and his fellow investigators, it has been demonstrated that the glycosuria following epinephrin administration is probably due to an increased mobilization of the glycogen in the liver, or in other words to an increased glycogenolysis, causing a temporary increased production of glucose and consequent hyperglycemia. Falta,

Eppinger and Rudinger have shown that the adrenals and chromaffin system produce a hormone that acts as an "accelerator" so far as carbohydrate metabolism is concerned. It is directly antagonistic in its action to the hormone of the pancreas, which inhibits glycogenolysis. In health we are supposed to have an even balance in the action of these two hormones and consequently the sugar in the circulating blood remains within normal limits. This balance may be disturbed in many ways producing hyperglycemia and glycosuria. There is an intimate relationship between the sympathetic (autonomic) nerves and the chromaffin system. In functional neuroses the latter system is stimulated through the autonomic nervous system and we have an overproduction of the accelerator hormone and consequent hyperglycogenolysis with resultant glycosuria. From experiments in Meyer's laboratory, in Vienna, it seems probable that the glycosuria following certain of the lesions of the central nervous system is produced as a result of overstimulation of the adrenals through the sympathetic nerves. It has been demonstrated that the nervous impulses pass down by way of the left splanchnic to the left adrenal and thence to the right. The glycosuria following Claude Bernard's famous "piqûre" experiment has been shown to be really of adrenal origin. The stimulation of the medulla is passed on to the adrenal by the sympathetic. If the left splanchnic is previously cut, glycosuria does not follow the piqure experiment. The fact that there is hypoglycemia after extirpation of the adrenals as well as in severe cases of Addison's disease shows the influence of these glands on carbohydrate metabolism.

H. Eppinger, of von Noorden's clinic, has shown that certain nervous patients have highly strung vagus systems, while in others this is entirely outweighed by the tonus of the sympathetic nervous system which antagonizes it. The symptoms in these persons are said to be respectively vagotonic and sympathicotonic. He has shown that the former are very sensitive to adrenalin and develop a considerable glycosuria with the injection of even one milligram of epinephrin. In the latter it takes a much larger dose to produce a glycosuria. Von Noorden believes that the vagus and sympathetic types are also present among diabetics. In one group the glycosuria is markedly increased by psychic or nervous influences, while in the other, these influences do not affect the glycosuria. The increased glycosuria in the former is supposed to be due to the mobilizing action of the increased epinephrin secretion on the glycogen of the liver.

(c) *The Hypophysis*.—Clinical experience for a long time has pointed toward a relationship between the pituitary gland and carbohydrate metabolism. It was long known that tumors in the region of the hypophysis, particularly in acromegaly, produced glycosuria. Out of 176 cases of acromegaly reported up to 1908, Borchardt found that glycosuria occurred in 35.5 per cent. of the cases. We owe to Cushing and his co-workers the demonstration of the fact that it is the secretion of the posterior lobe of the pituitary that affects carbohydrate metabolism. By removing the posterior lobe and a part of the anterior lobe in puppies the animals fail to grow properly; the sexual apparatus remains unde-

veloped; they become obese and their tolerance for saccharose becomes enormously increased. This hypopituitarism is an experimental counterpart of a type of infantilism in the human individual described by Fröhlich as "dystrophia adiposogenitalis." Cushing showed further that the subjects of "Fröhlich's syndrome" have an enormously increased tolerance for carbohydrates. The latter, instead of being completely metabolized, become converted into fat. The patients with this type of infantilism are known to have hypoplasia of the entire hypophysis, including the posterior lobe. Their tolerance for carbohydrates can be lowered and their adiposity diminished by administering extract of the posterior lobe.

The secretion of the posterior lobe of the hypophysis reaches the third ventricle by the infundibulum. It becomes mixed with the cerebrospinal fluid, and is probably absorbed into the circulation by way of the subdural spaces. It probably exerts its influence on carbohydrate metabolism by producing hyperglycogenolysis. It may do this directly. On the other hand, it may produce its effect by stimulating the hormone of the adrenals or by inhibiting the hormone of the pancreas. The fact remains that a hyperglycemia and glycosuria can be produced by the injection of posterior lobe extract into dogs. Simple manipulation of the stalk at operation frequently produces a glycosuria. This is no doubt due to increased absorption of posterior lobe secretion and is analogous to the exaggeration of the symptoms of hyperthyroidism immediately following thyroidectomy.

The glycosuria following fractures of the base of the skull may be in some cases due to disturbance of the posterior lobe secretion. In pregnancy there are certain signs of hyperpituitarism and some of the glycosurias of pregnancy may be due to hypersecretion of the posterior lobe during temporary hyperplasia of the whole gland.

It is a well-known fact that in the late stages of acromegaly (hypopituitarism) the subjects become obese, and in this stage of the disease there is an increased tolerance for carbohydrates. The adenomas of the anterior lobe, causing the acromegaly, produce a hypoplasia of the posterior lobe, thus explaining this increased tolerance to starches and sugars and the consequent tendency to adiposity. The discrepancies in the results reported concerning the presence or absence of glycosuria in acromegaly probably depend entirely upon the stage of the disease at which the investigation was made. The probability is that all acromegalics in the early stages have either a glycosuria or a diminished tolerance for carbohydrates. Cushing believes that one of the important functions of the pituitary is to regulate the assimilation limit for carbohydrates in the individual.

(d) *Thyroids and Parathyroids.*—Those who have had a wide experience with diseases of the thyroid gland have been impressed with the fact that in hyperthyroidism and hypothyroidism there is a marked disturbance of carbohydrate metabolism. Kraus, Ludwig, Chvostek and many others have observed that spontaneous glycosuria is not uncommon in exophthalmic goitre. Further, it has been shown that the administration of small amounts of carbohydrate in this condition

often causes a temporary glycosuria. In other words, in overactivity of the gland the tolerance for carbohydrates is reduced.

On the other hand, in hypothyroidism, cretinism and myxœdema, the occurrence of spontaneous glycosuria is extremely uncommon. Hirschl found in an outspoken case of myxœdema that the administration of 200 to 500 grams of grape-sugar did not produce alimentary glycosuria. Thus carbohydrate tolerance was increased two to five times. The administration of epinephrin is said by Falta not to produce glycosuria in thyroidectomized dogs. MacCallum demonstrated that the glycosuria following pancreatectomy is diminished by extirpation of the thyroid. McCurdy, Falta and others have found that extirpation of the thyroid raises the tolerance of animals for sugar, so that alimentary glycosuria is produced with difficulty, provided that the parathyroids are not disturbed. John King has produced experimental evidence tending to show that the expressed juices from the thyroid and pancreas break up glucose in much the same way as Cohnheim demonstrated for the juices expressed from the muscles and pancreas. Grey and De Sautelle have shown that the glycosuria in animals following administration of ether or chloroform is markedly diminished if the thyroid has been previously removed, demonstrating, as they believe, that when the restraining influence of the thyroid is removed the pancreas is more efficient for carbohydrate metabolism.

Eppinger, Falta, and Rudinger have shown that the parathyroids possess an opposite effect to that of the thyroids on carbohydrate metabolism. Underhill and Hilditch demonstrated that after excision of three of the four parathyroids in the dog the tolerance of the animal for sugar was greatly lowered, and that complete thyroparathyroidectomy, besides causing tetany, gave rise to glycosuria.

Diabetes and Organic Diseases of the Liver.—When one considers what an important part the liver plays in carbohydrate metabolism—being the great glycogen reservoir—it would be natural to expect that organic lesions of the liver would frequently be the cause of diabetes. Clinical experience, however, teaches us that the most extensive disease of the liver, such as carcinoma and cirrhosis, may occur without even a glycosuria appearing. Naunyn seems to be the strongest advocate of what he terms a “liver diabetes,” that is, where the diabetes is due to the organic change in this gland. He describes personal observations of cases of diabetes attributed to *cirrhosis* of the liver and to the liver disturbances accompanying *gall-stones*. He also draws attention to the frequency with which he has found glycosuria in individuals with enlarged livers, caused by *passive engorgement* secondary to cardiac disease. There does not seem to be sufficient evidence at the present time to justify the opinion that a true “liver diabetes” exists. Until a large number of cases of diabetes with organic disease of the liver and without microscopic evidence of disease of the islands of Langerhans are reported, we must support this contention.

Renal Diabetes.—The only cases known to be definitely of renal origin are those of “phloridzin diabetes,” experimentally produced by the administration of phloridzin. In 1886 von Mering discovered that

when phloridzin is administered by mouth or subcutaneously in man or animals a temporary glycosuria results. The amount of sugar in dogs may reach 18 per cent. The glycosuria continues in animals fed on nitrogenous diet, or in men when fasting, indicating that the sugar is in part manufactured from proteins. An important fact is that no hyperglycemia exists. That the glycosuria results from the phloridzin causing certain changes in the renal cells rendering them more permeable to glucose, is indicated by the fact that there is no increase of glucose in the blood; by failure of a hyperglycemia to occur after ligaturing the ureters or excising the kidneys; and by the observation of Zuntz, who found that when phloridzin is injected into one renal artery, glucose is excreted by the corresponding kidney immediately, while it does not appear in the urine of the opposite kidney until half an hour later, that is, until after it reaches that kidney through the general circulation.

Considerable doubt exists as to whether, clinically, the "renal diabetes" of Jacobi actually occurs. The instances of diabetes occurring in the course of chronic nephritis are usually cited in support of the view that a renal diabetes actually exists. Klemperer records a very suggestive case in which a patient with chronic nephritis excreted 0.35 per cent. of glucose. There was no accompanying hyperglycemia, nor did the latter occur even after the individual was fed on bread and glucose and excreted as much as 150 grams of sugar daily. In fact the blood showed a hypoglycemia. Naunyn reports 3 cases of diabetes in chronic nephritis, and inclines to the view that cases of renal diabetes occur, but admits that the question is still an open one. He cites the cases of glycosuria accompanying renal hemorrhages and chyluria, in support of the "renal diabetes" hypothesis.

Miscellaneous Factors.—Transitory glycosuria occasionally occurs in the course of acute fevers. It is not uncommon after the administration of ether, less so after chloroform. Hofmeister has produced a "hunger-diabetes" in dogs by cutting off all food for a few days. A clinical analogy to this is the glycosuria which occasionally occurs in severe cachexias and anemias. Patients suffocated by smoke or poisoned by carbon monoxide may have a temporary glycosuria.

In 1900 Hans Leo, after producing glycosuria in dogs by feeding them both fermented and unfermented urine, advanced the view that diabetes was due to some unknown toxin. There has been no further evidence to substantiate this view.

Disturbances of Metabolism.—The immediate cause of diabetes is the development of a hyperglycemia; that is, an excess of glucose in the circulating blood. The explanation for the occurrence of this is the problem which is still in need of a solution. As the metabolic disturbances in diabetes have to do mainly with the warehousing of the carbohydrates, this will probably be best appreciated by first reviewing the fate of the carbohydrates in normal metabolism.

The hexoses mainly concern us in a discussion of both normal and pathological carbohydrate metabolism. The hexoses, in general terms, may be described as carbohydrates, the molecules of which contain the carbon atoms to the number of six or multiples thereof, and the hydrogen

and oxygen atoms in the proportion in which they form water. They are classified according to the number of carbon atoms they contain:

1. The *monosaccharides*, or *glycoses*, having the general formula $C_6H_{12}O_6$. These include grape-sugar, also called dextrose or glucose (dextrorotatory); fruit-sugar or levulose (levorotatory); galactose and mannose (both dextrorotatory). All these ferment and reduce alkaline copper-sulphate solutions.

2. The *disaccharides*, or *saccharoses*, possessing twelve atoms of carbon in the molecule, and having the formula $C_{12}H_{22}O_{11}$. These are formed by the combination of two molecules of a monosaccharide with the loss of a molecule of water. They include cane-sugar or saccharose; milk-sugar or lactose; and maltose. With the exception of cane-sugar, all reduce alkaline copper-sulphate solutions. All are dextrorotatory, but do not ferment without being split up by dilute mineral acids, etc.

3. The *polysaccharides*, or *amyloses*; these are the anhydrides of a combination of many molecules of monosaccharides, and possess the general formula, $(C_6H_{10}O_5)_n$. They include starch, glycogen, and dextrin (all dextrorotatory); inulin (levorotatory); cellulose, and animal gum (inactive). They do not reduce alkaline copper-sulphate solutions and do not ferment without being previously split up.

Normal Carbohydrate Metabolism.—(a) *Formation of Glucose from Carbohydrates.*—The carbohydrates in the food undergo a series of changes during ingestion, as a result of the action of the diastatic ferments in the saliva, pancreatic juice, and succus entericus. Possibly some changes also occur in the process of absorption. Starch, the most abundant article in our dietary, is eventually converted into maltose, or maltose and dextrin, after passing through a series of intermediate stages. The maltose and dextrin are further converted into dextrose by the sugar-splitting enzymes of the intestinal mucous membrane. Cane-sugar is hydrolyzed into dextrose and levulose, and milk-sugar probably undergoes a similar change to dextrose and galactose, although of this we are not so certain. The carbohydrates of our food are eventually absorbed in the form mainly of dextrose (glucose) or dextrose and levulose. These sugars are absorbed directly into the portal capillaries and not into the lymphatics. As a result of carbohydrate digestion the portal vein conveys to the liver a stream of sugars consisting mainly of dextrose, but also of smaller quantities of levulose and galactose, and there, by a process of dehydration, the liver-cells convert them into glycogen as follows: $C_6H_{12}O_6 - H_2O = C_6H_{10}O_5$. The surplus that is not required for the immediate use of the economy is stored up in the liver as glycogen. According to the generally accepted view of physiologists, this glycogen is reconverted into glucose, probably by the action of a special enzyme produced by the liver cells. This glucose reaches the general circulation by the hepatic veins, and is conveyed to the tissues, where it is oxidized, producing heat and energy. This glycogenic function of the liver is generally accepted, though it has been vigorously opposed in certain quarters.

(b) *Formation of Glucose from Ingested and Body Proteins.*—A great deal of information has been acquired concerning the relation between

the urinary nitrogen and sugar elimination in the fasting and meat-fed diabetic organism. The dextrose to nitrogen ratio (D:N) is a key to the problem of the quantity of sugar which can be derived from protein metabolism. Minkowski discovered that depancreatized dogs, whether fasting or fed on meat, showed a constant elimination of 2.8 grams of dextrose for each gram of nitrogen in the urine. This ratio (D:N : : 2.8:1) was the average obtained from several dogs on twenty-two different days. He showed that 45 grams of glucose is formed from every 100 grams of protein metabolized in the body. Nolan and Lusk have demonstrated that in phloridzin diabetes the D:N ratio is 3.65:1. Falta has shown that this same ratio may exist in dogs after the removal of three of the parathyroids and the pancreas. It is now generally conceded that the D:N ratio in most diabetics who have no tolerance for carbohydrates is 2.8:1, while in a few cases it has been found to be 3.65:1. The former represents a formation of 45 grams of dextrose from 100 grams of meat protein, the latter one of 58 grams of sugar from meat protein. The dextrose in the 2.8:1 ratio is spoken of as α -dextrose, whereas that in the 3.65:1 ratio is called β -dextrose. The β -dextrose represents the additional 13.6 per cent. of protein, when the ratio 3.65:1 exists. The ratio depends upon the combustion or non-combustion of the β -dextrose. If the latter burns, it must do so as a complex, for as free dextrose it would be eliminated in the urine (Lusk). The formation of dextrose from protein is now a well-established fact. Further evidence is afforded by the fact that severe diabetics often excrete sugar when on a similar diet.

(c) *Formation of Dextrose from Fat.*—The balance of opinion at the present time is opposed to the view that sugar is ever formed from fat. There is evidence that it can possibly be formed from glycerin and the neutral fats. Von Noorden is the strongest advocate in favor of the view that dextrose may be derived from fat. He thinks that the quantity is always very small and that the transformation is more likely to occur in the diabetic individual. Ringer has recently published the results of experiments which show that dextrose may be formed from the higher fatty acids.

The liver is capable of storing up glycogen to the extent of 14 per cent. of its own weight. The amount it contains depends on several factors. Prolonged fasting, continuous physical exertion, and high temperature, rapidly deplete its supply of glycogen. The latter is greatest in amount on a diet rich in carbohydrates. The liver is not the only seat for the storage of glycogen, however. The other great reservoir is the muscular system; and it is estimated that the quantity in the muscles practically equals that stored in the liver. When conditions favor the depletion of the supply of glycogen it is found that the muscles give up their supply much less readily than does the liver. The source of the muscle glycogen is not definitely known, but presumably it is formed from the glucose brought to the muscles by the blood.

It is not definitely known whether dextrose normally circulates in the blood as such or in combination. Loewi believes it is in loose combination with a colloid substance. He holds that the colloid sugar cannot pass through the glomerulus. If, for any reason, sugar accumulates in

the blood above the combining power of the colloid, then the crystalloid dextrose readily passes through the kidney. Lusk supports Loewi's view.

It has been clearly shown that the amount of glucose in the circulating blood normally varies within quite narrow limits, namely, between 0.1 and 0.2 per cent., Jacobson claiming that the average is 0.07 per cent. Cammidge and others consider 0.1 per cent. as the upper limit for normal, believing that a glycosuria will occur when the circulatory blood contains more than this amount. This constancy is remarkable because we would expect that when carbohydrates are ingested in large quantities the blood would contain more glucose than when they are taken in smaller amounts. This is not the case, however, for the percentage of sugar in the circulating blood remains in normal individuals constantly within the narrow percentage limits mentioned above. This naturally leads us to consider the fate of the carbohydrates under conditions which may be considered as normal variations.

(a) *In Ordinary Nutrition.*—In a healthy person, on a usual mixed diet and taking a moderate amount of exercise, the carbohydrates are always on hand and are always in demand. By their combustion, presumably for the most part in the muscles, they produce heat and energy. Owing to the fact that normally there is no loss of sugar in any of the excretions, excepting in the urine in the minutest traces, and owing to the interposition of the two carbohydrate reservoirs, the liver and muscles, the percentage of glucose in the circulating blood remains practically constant.

(b) *When the Supply of Carbohydrates is Insufficient and the Demand Excessive.*—For a few hours or days under these conditions the glycogen in the liver and muscles is called upon, and makes up for the deficiency of the carbohydrate intake. In this way the percentage of glucose in the circulating blood is kept within normal limits. Eventually the glycogen is entirely used up, yet the blood contains the normal amount of glucose. This has been thought by some to be due to the conversion of the body-fat into glucose, but the phenomenon is more likely explained by the conversion of the body-protein into glucose.

(c) *When Carbohydrates are Ingested in Excess of the Needs of the Body.*—The fate here depends on circumstances. Within certain limits, the excess in carbohydrates can be stored up in the liver and muscles as glycogen. The limit of this storage capacity is eventually reached, for von Noorden states that the human organism is capable of storing up only about 300 grams of glycogen. Results will now vary according to whether the carbohydrates are ingested in moderate excess over a considerable interval, or in enormous quantities in a short period of time. In the former case the excess of carbohydrates is converted into fat which is deposited in the connective tissues, and no hyperglycemia occurs. When, however, there is a sudden ingestion of an enormous amount of carbohydrates, the liver and muscles cannot store it all up as glycogen, nor can the organism convert it all into fat. An excess of glucose accumulates in the circulating blood. When the blood contains more than 0.2 per cent. of glucose a hyperglycemia exists, which always results in the appearance of glucose in the urine.

The form of glycosuria produced in the manner just described is known as *alimentary glycosuria*. This may be considered a physiological process, and must not be confused with true diabetes. The quantity of sugar that can be ingested without its appearing in the urine is designated by Hofmeister as the *assimilation limit*. This varies in normal persons according to the individual and according to the sugar ingested. Naunyn called this form of glycosuria *glycosuria e saccharo*. The assimilation limit for a single dose of the various sugars given on a fasting stomach is as follows: For dextrose or glucose, 150 to 200 grams; for levulose, 140 to 160 grams; for cane-sugar or saccharose, 150 to 200 grams; for lactose it is lower, 120 grams with some individuals, and as little as 60 grams for others. In determining the tolerance of an individual for carbohydrates it is customary to give 100 grams of glucose in 250 cc. of water either on an empty stomach in the morning, or, as Naunyn prefers, two hours after a very light breakfast consisting of 250 cc. of coffee with milk and 80 to 100 grams of bread. With either method, if glucose appears in the urine the tolerance of the individual for carbohydrates must be considered lowered. When the sugars are taken after a light meal the limit is higher. It is well to emphasize here that, in a healthy person, sugar never appears in the urine after the ingestion of even enormous quantities of starch. Digestion and absorption take so much time that a sudden flooding of the blood with carbohydrates cannot take place. When a glycosuria does occur after the ingestion of starch it is called *glycosuria ex amylo*.

It should always lead the physician to suspect that a true diabetic condition exists, for it means that the assimilation limit is very much lowered.

Manner in Which the Carbohydrates are Oxidized in the System.—We have until a recent date been almost entirely in the dark as to how and where the glucose of the blood is ultimately burnt up. At one time it was thought that it was oxidized in the lungs. Subsequently, the body tissues, particularly the muscles, have been held to be the seat where the carbohydrates are oxidized, yielding energy and heat, and resulting in the production of carbonic acid and water. Lépine and Barral held that this "glycolysis" was affected through the agency of a glycolytic ferment produced by the pancreas as an internal secretion. Arthus denied the existence of such a ferment in the circulating blood, and held that the enzyme is merely a postmortem product resulting from the disintegration of the red-blood corpuscles.

It is now conceded that the muscles constitute the furnace in which the glucose of the circulating blood is eventually burnt up. How this is brought about is still largely a matter of speculation. As a result of experimental work published in 1903 and 1904 Cohnheim suggested that a correlation existed between the internal secretion of the pancreas and a muscle enzyme, to which it acted as an amboceptor. For the muscle enzyme to be capable of destroying sugar it is necessary that it be first activated by the pancreatic ferment. This attractive theory has not received general support and for the time being, at least, must be considered with skepticism.

Metabolic Changes in Diabetes.—Having reviewed the main features of carbohydrates metabolism in health, it is now in order to see what variations occur in diabetes mellitus. Hyperglycemia, or excess of glucose in the blood, is the most constant and striking evidence of disordered metabolism in the disease. Naunyn states that he knows of no case of diabetes in man without a hyperglycemia, with the exception of Klemperer's case of diabetes in chronic nephritis, where the glucose in the blood was said to be subnormal. In phloridzin diabetes, which is a true renal diabetes, there is no hyperglycemia, and often the glucose in the blood is decidedly below normal. The great problem is to ascertain why this hyperglycemia occurs. Whereas the blood normally contains from 0.07 to 0.1 per cent. of glucose, with 0.2 per cent. as the maximum normal amount, in diabetes the glucose may reach 0.6 per cent., according to determinations made by Pavy and by Seegen. Naunyn found 0.7 per cent. in one case.

Another very striking and almost constant metabolic disturbance in diabetes is the failure of the liver to store up glucose in the form of glycogen (zoöamylon), a condition to which Naunyn has given the term "dyszoöamylie." The amount of glycogen in the liver is usually reduced, or it may be entirely absent. Naunyn says that the evidence at hand is not sufficient to decide the question as to whether the deficiency of the liver in glycogen is due to failure of the liver cells to convert glucose into glycogen, or mere failure of the liver cells to store it up when received. This poverty in glycogen is also a striking feature in the experimental glycosuria following medullary puncture and extirpation of the pancreas. It is an interesting fact that a diabetic can store up glycogen in his liver from ingested levulose, whereas there is no conversion from ingested glucose. This failure of the liver cells to store up glycogen is very closely related to the production of the hyperglycemia. Why this power is lost is not yet understood.

The modern view that an excess of epinephrin causes an increased mobilization of glycogen, or, in other words, an increased glycogenolysis, may throw considerable light on this point.

So long as a diabetic is still capable of warehousing moderate amounts of carbohydrates there is no special disturbance of *protein metabolism*. While in the healthy individual, and in mild diabetics, the supply of carbohydrates derived from protein metabolism can be made use of to protect the tissues from further destruction; in the severe type this is not the case, for when the protein sugar is withdrawn from the tissue cells there is a large increase in protein metabolism, and consequently in the nitrogen output in the urine. Mendel and Lusk found in a severe diabetic that the ingestion of broths containing 7.7 grams of nitrogen was followed by an elimination of 21.7 grams of nitrogen in the urine, or a loss of body nitrogen of 14 grams, and that nitrogen equilibrium could only be maintained by giving 27 grams of protein nitrogen in the food. Minkowski, Falta, and Lusk have shown that the D : N ratio in diabetics who have completely lost their power to warehouse carbohydrates is constant, either 2.8 : 1 or 3.65 : 1, no matter how much protein is given, and is in no way dependent upon variations in the amount of fat in the

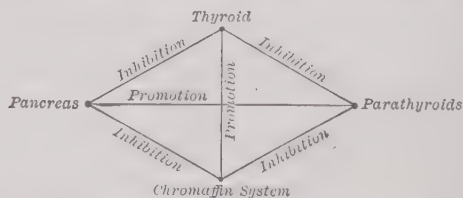
diet. Further evidence of the disordered protein metabolism is found in the great increase in the quantity of ammonia and endogenous purin bodies in the urine.

In the defective *metabolism of fats* lies the great danger in the severe forms of diabetes. There is an inability on the part of the organism to properly burn up the hydrocarbons. The chief product of this incomplete combustion of fat is β -oxybutyric acid, from which the acetone and diacetic acid are derived, and which is the cause of diabetic coma.

Theories of Diabetes Mellitus.—In view of what we now know, diabetes must be regarded not as an entity, but as a symptom-complex dependent upon a variety of causes and having an intimate relationship with the various internal secretions. Many of our conceptions concerning carbohydrate metabolism in diabetes are based on theoretical consideration, which may, however, eventually prove true by actual proof. At the present time, therefore, it is best not to be too dogmatic in attempting to explain the glycosuria in all cases of diabetes. The outstanding feature to be constantly kept in mind is that control of sugar formation and its distribution takes place in the liver. Glycosuria, with the exception of phloridzin diabetes, is always dependent upon a hyperglycemia, and this excess of sugar in the circulating blood is due to the influences which control glycogenolysis.

1. *Theory that Diabetes is Dependent upon a Disturbance of the Correlation of the Functions of the Ductless Glands. Theory of Overproduction of Sugar.*—As this most recent conception of the cause of diabetes has already been taken up with some detail, only the essential points will be brought out here. Eppinger, Falta, and Rudinger have shown that the ductless glands may be divided into two groups according to the action of their hormones. There is (1) an *accelerator* group, and (2) an *inhibitory* group. The thyroid, pituitary and suprarenals (chromaffin system) belong to the former, since it has been shown, partly as a result of injections of preparations from these glands and partly in consequence of interference with the function of the glands (removal), that all three increase protein metabolism, that the adrenals cause mobilization of the carbohydrates, and that the thyroid causes increased fat absorption. To the inhibitory group belong the pancreas and parathyroids, since both retard protein exchange, and both restrain the mobilization of carbohydrates, in each instance the pancreas being the more powerful.

The inter-relation of the functions of the pancreas, thyroid, parathyroids, and chromaffin system may be represented as follows:



Evidence tends to show that the hormones of the pancreas and adrenals are antagonistic in their action so far as carbohydrate metabolism is

concerned. Both profoundly influence the mobilization of glycogen in the liver. The former retards glycogenolysis, whereas the adrenals accelerate the mobilization of liver glycogen, that is, hastens glycogenolysis. In health and when both glands are functioning normally, the action of each hormone balances the other and the glycogenic function of the liver is carried on normally, no hyperglycemia occurs and consequently no glycosuria.

According to this conception the glycosuria following extirpation of the pancreas may be considered a negative pancreatic diabetes and a positive adrenal diabetes, for the normal inhibitory action of the hormone of the pancreas is removed, whereas the mobilizing power of the adrenal hormone on the liver glycogen is increased by hyperfunction of the chromaffin system. As Cammidge suggests, the latter results partly from the removal of the inhibitory action that the pancreas normally exerts on the chromaffin tissue, and partly as an indirect effect of the absence of the similar inhibitory action that the pancreas has on the thyroid, which is thus at liberty to exert its stimulating action on the chromaffin tissue unchecked. At the same time there is excessive metabolism of proteins, fats, and carbohydrates as a consequence of the hyperfunction of the thyroid. This explanation would account for the greater intensity of pancreatic as compared with other forms of experimental diabetes.

Clinically, destruction of the islands of Langerhans is supposed to produce glycosuria in the same way. The pancreatic hormone being absent, there is nothing to check the mobilizing action of the adrenal hormone, and increased glycogenolysis and consequent hyperglycemia and glycosuria occur. The transitory glycosurias in neurotic persons and the increased sugar output in diabetes under emotional disturbances is explained by the intimate connection between the adrenals and the sympathetic system. Stimulation of the sympathetic system causes increased adrenal function, which for the time being is not counterbalanced by the internal secretion of the pancreas, and hyperglycogenolysis with resultant glycosuria occur. If one accepts the above views it is easy to account for the glycosurias following the injection of epinephrin.

The glycosuria following Bernard's "piqûre" experiment is really of adrenal origin. Impulses pass to the adrenals by way of the sympathetic causing an increased secretion of epinephrin and consequent hyperglycemia.

Removal of the thyroid gland (or spontaneous myxœdema) leads to hyperfunction of the pancreas, owing to the removal of its inhibitory function on that gland, while at the same time it diminishes adrenal action, from the absence of the promoting effect of the thyroid on the chromaffin tissue. This accounts for the increased tolerance in myxœdema. Hyperthyroidism (exophthalmic goitre) produces the opposite effects, causing relative pancreatic insufficiency and increased adrenal activity, with a tendency to glycosuria.

Underhill and Hilditch have shown that after parathyroidectomy there is a lowering of carbohydrate tolerance. This is probably due in part to the inhibitory effect that the parathyroids have on the adrenals

and in part due to the absence of their inhibitory action on the thyroids, which normally promote adrenal action.

Cushing and his associates have shown that in hyperpituitarism there is either a glycosuria or a lowered tolerance for carbohydrates and that in hypopituitarism an increased tolerance exists. The hypersecretion of the posterior lobe of the pituitary is believed to cause glycosuria by bringing about a hyperglycogenolysis. The secretion of the pituitary has an inhibitory action on the pancreatic hormone. If, therefore, the posterior lobe of the pituitary is overactive this inhibitory action is increased and the restraining influence the pancreas has on glycogenolysis is impaired, the mobilization of the glycogen becomes more active and a hyperglycemia and glycosuria result. Cushing and Jacobson have found that animals who have acquired a high sugar tolerance after extirpation of the posterior lobe of the pituitary may subsequently be deprived of the pancreas without glycosuria developing.

From the above consideration it will be seen that the factors that control carbohydrate metabolism are very numerous. Von Noorden and his associates are the strongest supporters of the view that carbohydrate metabolism is powerfully influenced by the interaction of the hormones of the ductless glands.

What has been said in this connection might be advanced as an argument in favor of the view that diabetes is due to an overproduction of sugar. In a broad sense this is true, for with this modern concept of diabetes it seems to matter little what the primary exciting factor may have been, it always leads eventually to a hyperglycogenolysis or increased mobilization of the glycogen in the liver. This, in all instances, seems to be due either to a lessening of the restraining power of the pancreatic hormone or to a stimulation of the acceleration action of the adrenal hormone.

2. *Theory of Underconsumption and Deficient Oxidation of Glucose.*—Much investigation has been carried on in order to determine whether the hyperglycemia and consequent glycosuria in diabetes are dependent upon deficient oxidation of glucose in the muscles and other tissues. The respiratory coefficient has been utilized in order to help in solving this problem. This coefficient is determined by dividing the volumes of CO_2 output by the O_2 intake, and for a healthy individual on a mixed diet is represented by the fraction 0.9. Although Voit and Leo years ago claimed that there was no reduction in the respiratory coefficient, the more recent work of Benedict and Joslin indicate that it is reduced. These investigators utilize this coefficient as a means of determining the severity of the diabetes. They conclude that a respiratory coefficient above 0.74 indicates a fairly liberal supply of glycogen stored in the body; whereas a coefficient of 0.70, or below that, shows that the patient has no available carbohydrates, and has lost in a measure the power of storing them. Weintraud and Laves found that the addition of small quantities of carbohydrates to the diet of diabetics raises the respiratory coefficient much less than in health. They conclude that this is evidence that the glucose is not properly oxidized in the tissues.

Lactic and glycuronic acids are considered by most physiologists

to be intermediate products in the combustion of glucose. Glycuronic acid, like glucose, is found in minute traces in normal urine. Mayer has found the glycuronic acid excretion considerably increased in diabetes, and, as he has found it also increased in conditions of suboxidation, he thinks he has demonstrated conclusively that diabetes is due to deficient oxidation in the tissues. The lowered respiratory coefficient in the severe cases of diabetes is no doubt due in part to the inability of the system to oxidize fats.

Reference must be made here to Cohnheim's view that the glucose of the blood is normally consumed in the muscles by the activation of a muscle pro-enzyme by a pancreatic enzyme. The attractive theory, based on this view, that the hyperglycemia is due to the absence of the pancreatic activator, has been pretty generally abandoned.

We must not be too dogmatic in attempting to explain the hyperglycemia of diabetes. Views are constantly changing. For the moment, the view that it is due to increased mobilization of the liver glycogen has the upper hand. According to this view this increased glycogenolysis is dependent either upon influences that stimulate the accelerator hormone of the chromaffin system or lessen the restraining influence of the pancreatic hormone.

Pathology.—The etiology and pathology are so closely related that it is almost impossible to discuss one without the other. In the section on etiology those morbid lesions which were believed to be the cause rather than the result of the diabetes have already been considered. Thus the organic lesions of the *nervous system*, *liver*, and *pancreas* which are so important in the etiology of diabetes, have been fully discussed. The changes not already mentioned and particularly those which are regarded as the result of the disease will now be briefly considered.

The *blood* always shows a hyperglycemia. The only exceptions to this rule are the cases of phloridzin diabetes and the other rare instances of so-called "renal" diabetes which have been described by Kemperer and Naunyn. In these cases there is a hypoglycemia and the blood is often concentrated. The specific gravity may be increased or diminished, according to the water content. In cases with marked polyuria, in which the watery constituents of the blood are depleted, the red cells may be 6,000,000 per cmm. or more. The latter react differently from those of normal blood with certain aniline dyes. Bremer found that smears of diabetic blood, heated for six to ten minutes at 135° C. and immersed for one to two minutes in a 1 per cent. aqueous solution of congo-red, remained unstained, while smears of normal blood take the red stain. The red cells of diabetic blood also stain differently with eosin and methylene blue. The leukocytes are usually normal in number, or increased only in proportion to the concentration. The writer has observed a leukocytosis of from 18,000 to 25,000 in diabetic coma. The leukocytes contain glycogen. The alkalinity is reduced, particularly in coma. This is occasioned by the presence of β -oxybutyric and diacetic acids. Acetonemia may occur. *Lipemia* occasionally occurs. The fat may be detected in the form of numerous minute dancing granules in the serum in thick preparations of fresh blood. The separated serum

has a decided milky appearance. Fraser, in 1903, reported a case in a diabetic with a fatal coma. The percentage of fat in the blood was 16.44 per cent. Fischer recorded a case with 18.12 per cent., the highest ever reported. According to Becquerel and Rodier, blood normally contains from 0.16 to 0.325 per cent. of fat. Exudates in the serous sacs may be turbid with fat. The lipemia has been attributed to the overingestion of fats, to fatty degeneration of the viscera, and to deficient lipolysis. In Fraser's case, the appearance of the lipemia was coincident with a marked reduction in the sugar of the blood, and he thinks that the fat may be derived from the glucose. The fat droplets take the characteristic stains with Sudan III and osmic acid.

No characteristic changes are to be found in the *gastro-intestinal tract*. Frerichs frequently found a thick layer of a fungus growth in the mucous membrane of the fauces and œsophagus. Occasionally the stomach has been found dilated. Swelling, redness, and ecchymoses of the gastric mucosa, have been noted. Tuberculous ulceration of the intestine may occur when there is a pulmonary tuberculosis.

The *heart* may be hypertrophied, but this is rare. The myocardium is often pale and soft. In old-standing cases, advanced fatty degeneration of the muscle-fibres is common. Pericarditis and endocarditis rarely occur. Arteriosclerosis is rather common.

Of the *pulmonary* lesions, tuberculosis is probably the most common. The tissues of the diabetic seem to furnish a specially good medium for the growth of the tubercle bacillus. Acute bronchopneumonia and lobar pneumonia may occur, and either may terminate in gangrene. The writer has seen one case of bronchopneumonia terminate in abscess formation. Grohe, Kuhne, and Ehrlich, have shown the cells of the pneumonic exudate to be rich in glycogen. A chronic non-tuberculous interstitial pneumonia has been described. So-called fatty emboli of the pulmonary arteries occur in coma.

The *liver* is usually somewhat enlarged, and fatty degeneration is common. The form of cirrhosis designated by Hanot as *cirrhose pigmentaire diabétique*, which is one of the lesions of hemochromatosis in which diabetes may develop as a late manifestation, has already been described. Poverty of the liver in glycogen is a striking feature. The *pancreatic* lesions have been described. Pancreatic calculi or gall-stones pressing on the duct of Wirsung occasionally occur. They lead to secondary sclerotic changes in the pancreas and produce the most typical form of pancreatic diabetes. There are no changes in the gland that are regarded as secondary to the disease.

The *kidneys* are often enlarged. The most characteristic change is a hyaline degeneration of the epithelial cells of Henle's loop, described by Armanni and sometimes spoken of as the lesion of Armanni. The affected cells present a swollen, transparent appearance, as if transformed into large hyaline vesicles. The nuclei stain well and are pushed to the periphery. Cantanni and others have confirmed Armanni's observations. Ehrlich and Frerichs have described a glycogenic degeneration of the same cells as are involved in Armanni's lesion. The degeneration can be demonstrated macroscopically by treating the kidney section with

Lugol's solution, the affected portion taking on a red color. Straus holds that the hyaline changes described by Armani and the glycogenic changes described by Ehrlich and Frerichs, are really of the same nature. In some cases he has demonstrated the hyaline changes without finding glycogen present. In such cases, he thinks that the glycogen has been present at one time, but has disappeared before death, leaving only the hyaline changes. Ebstein described a necrosis of the renal epithelial cells, similar to the coagulation necrosis of Weigert in other diseases. Interstitial and parenchymatous nephritis may occur, but there is no reason to believe that diabetes is the cause of the nephritis in these cases. A *cystitis* usually occurs. It has been attributed to irritation by the saccharine urine, but it is more likely due to bacterial infection.

Of the lesions of the *nervous system* not already described, Saundby states that congestion and œdema, and thickening of the membranes of the brain, may occur. Williamson, Sandmeyer, and Kalms have described a degeneration of the posterior columns of the cord similar to the sclerosis of these tracts in *tabes dorsalis*. Williamson states that the lesion is best seen with the naked eye, when the affected portions appear much paler than does the healthy white matter. These changes are attributed to the action of some toxic agent. The peripheral nerves, particularly those of the lower extremities, may be the seat of an interstitial inflammation, with secondary degeneration of the axis cylinders of the nerve fibres. This *neuritis* may cause clinical symptoms.

Symptoms.—Various writers have been disposed to recognize certain clinical types and thus *acute* and *chronic* cases are described. The acute cases generally occur in children and young adults, the emaciation being marked and the course very rapid. The chronic cases, usually occur in persons who develop the disease after the fortieth year, and in middle-aged and elderly obese individuals. The acute cases, however, may occur in the aged. Osler reports a man aged seventy-three years in whom the entire course of the disease was less than three weeks.

There are the *mild* and the *severe* cases. According to Naunyn, if the glucose disappears with the patient on a non-carbohydrate diet, the case belongs to the former type. If, on the other hand, he continues to excrete glucose, the case is a severe one, for it means that sugar is being produced from the body proteins. The presence of a high ammonia excretion and of β -oxybutyric acid and its derivatives, acetone and diacetic acid, is also indication of a severe type. Further we have the *fat* or *lipogenous* (*diabète gras*) and the *emaciated* (*diabète maigre*) cases. Lancereaux believed the latter were caused by lesions of the pancreas. *Exogenous* and *endogenous* cases have been described. The former embrace the cases in which there is some external exciting cause. The latter, according to Strümpell and others, include those in which there is no apparent external etiological factor, or any evident organic lesion, but in which the disease is thought to be due to some developmental abnormality. We have also the *neurotic* cases due to injuries or functional disorders of the nervous system. There is no fundamental difference in any of these cases, and no satisfactory classification, along the lines indicated, seems possible.

Although the disease is usually accompanied by a certain group of symptoms which especially characterize it, and which may be so abrupt in their onset that the patient can state the date of their appearance with considerable accuracy, yet these may for a long time remain in abeyance, and may even never become a prominent feature. Thus the polyuria, thirst, increased appetite, emaciation, and weakness, may not be sufficiently marked to attract the patient's attention. The first intimation of there being anything wrong may be a failure in vision. On the other hand, the patient may consult the family physician for an obstinate general or localized pruritus as the first symptom. Similarly, a furunculosis, a severe neuralgia, or impotence, may cause the patient to seek advice. Occasionally general weakness, nervousness, slight change in temperament, mental hebetude, and inability to apply himself to business, may antedate the characteristic symptoms. Too often, unfortunately, the disease gets a firm foothold and has seriously impaired the general health before it is finally recognized.

Polyuria is the symptom most frequently first complained of by the diabetic. In the acute cases, the patient asserts positively that the quantity of urine suddenly became greater, and that he is obliged to get up frequently at night to pass urine. The increase in the quantity of urine is referable to the hyperglycemia. Owing to the increased quantity of glucose in the blood, the latter becomes hyperisotonic, and the fluids of the tissues are absorbed into the circulation more rapidly than in the normal individual, and consequently more water is secreted by the kidneys. The amount of urine may reach 10 to 20 liters daily in the severest cases, although it is rare to see cases in which more than 10 liters is voided in the twenty-four hours. The amount usually bears direct relationship to the percentage of sugar excreted. In certain cases there may be no increase in the urine when glycosuria is present.

Thirst, or polydipsia, may be extreme, and may be complained of as early as, but more often very soon after, the polyuria. It is indirectly traceable to the hyperglycemia, and directly to the desiccation of the tissues already described. It bears a definite relationship to the polyuria.

Increased appetite (bulimia or polyphagia) is a frequent symptom, particularly in the very acute cases. In the milder forms, and in the advanced stages of the severe type, this symptom may be wanting. There may even be loss of desire for food. Notwithstanding the enormous amount of food eaten, progressive emaciation is the rule, especially in the young individual. The increased appetite and the emaciation are largely dependent upon the same causes—the failure of the diabetic organism fully to utilize the carbohydrates of the food. The nutritive changes in diabetes are interesting and deserve some consideration. An individual doing light work requires about 40 calories for each kilo body weight daily, although the recent work of Chittenden seems to indicate that this caloric requirement is too high. Thus a person of average weight would require food to yield 2400 calories for his nutritive needs. Let us suppose this individual to be suffering from diabetes and to be taking a mixed diet including proteins, fats, and carbohydrates, in the following proportions with their caloric equivalents: 160 grams

of albumin, yielding 656 calories; 110 grams of fat, yielding 1023 calories; and 240 grams of carbohydrates, yielding 984 calories. This diet, therefore, would provide a total of 2663 heat units, or 263 more than would be required by the individual were he perfectly healthy. Let us suppose, however, that he is excreting 140 grams of sugar daily. He would therefore lose each day nutritive material to the value of $140 \times 4.1 = 574$ calories. The food of this diabetic consequently would have the value of only $2663 - 574 = 2089$, a deficit of 311 calories. The body, therefore, in order to meet the requirements of energy and heat production, must have consumed of its own substance to the value of 311 calories. The tissues drawn on for fuel material to make up for this caloric deficit are, of course, the albumins and fats. By estimating the amount of nitrogen in the food and in the urine and feces, it is possible, accurately, to determine the exact proportion of body-fat and albumin consumed daily to make up for the caloric loss resulting from the failure of the organism to utilize all the ingested carbohydrates owing to a considerable quantity being eliminated in the urine as glucose. This consumption of his own body-fat and albumin necessarily occasions a progressive loss in weight, and the hypothetical case illustrates how the emaciation is brought about. The latter will continue unless the diet is so regulated as to prevent a loss of sugar in the urine. Von Noorden explains the polyphagia in the following way: "The sufferer from this disease whose diet is not regulated by medical advice, swallows great quantities of food, including much carbohydrate. The 'stomach hunger' is momentarily stilled, but quickly returns, for 'tissue hunger' is not satisfied. The inordinate appetite of the diabetic disappears only when the useless carbohydrates are cut off and their place supplied by albumin and fat. When this is done the emaciation of the patient comes to a halt, with relief of the polyphagia."

The face is often of a deep red color. The skin of the entire body in the majority of cases is dry and harsh. This is due to the fact that the sweat, as is the case with nearly all the secretions, with the exception of the urine, is diminished in amount. The skin may be moist, however. In cases complicated by pulmonary tuberculosis, sweats may occur, and they have been known to alternate with polyuria. The nails are often brittle, and the hair thin and dry. There may be some irritability of temper. There is a strong tendency for the individual to become morose or even hypochondriacal. Some complain of extreme drowsiness during working hours. The temperature in uncomplicated cases is usually subnormal. The pulse is generally increased in frequency, with the pulse-tension above normal. Joslin has laid emphasis on the increased pulse frequency and attributed it to increased protein metabolism.

The mouth is dry, due to the thirst and to the diminished salivary secretion. The saliva is less alkaline than in health, and that collected from Steno's duct is usually acid in reaction. Frerichs, von Noorden, and Mosler found the saliva almost without exception free from sugar. Frerichs demonstrated sugar in one out of nine cases. The tongue is usually dry and red, and often has a glossy appearance resembling that in psoriasis linguæ. The digestion, notwithstanding the enormous

quantities of food taken, is, as a rule, good. Obstinate constipation is the rule. The eyesight, owing to the ocular complications, is often defective. Pain in the lumbar region is often an annoying symptom even early in the disease. Cramps in the calves of the legs occasionally cause much discomfort. Owing to the lowered vitality of the tissues, and owing to the latter being richer in sugar than normally and consequently being a better nutritive medium for the growth of organisms, wounds heal less readily and are much more liable to become infected. In patients with secondary lesions of the cord or peripheral nerves of the lower extremities a sensation of a "giving away" of the knees may be complained of. This occasionally occurs, however, even without nervous manifestations.

Loss of sexual desire and power in men is common, and may be an early feature. It may reach the grade of actual impotence. Sexual power may return, according to Seegen, with improvement in the patient's other symptoms while under treatment. Occasionally increased sexual desire with power persist throughout the disease. In severe cases of diabetes in women the sexual desire is much impaired, but in mild cases in elderly women it is said to be often increased. Amenorrhœa is not uncommon, and may occur early in the disease.

The Urine.—The amount has been considered under polyuria. It is usually extremely pale and clear. The quantity and pallor generally bear a direct relationship to the percentage of sugar present. Occasionally one sees diabetic urine of quite deep color. In these cases there is little or no polyuria. It often has a suggestive greenish tint, and may, when shaken, have a syrupy consistency. It has a sweet taste, and in severe cases with threatening coma, may have a sweetish, fruity odor, owing to the presence of acetone. The specific gravity usually ranges between 1.025 and 1.045. A pale urine with a specific gravity above 1.025 should always lead one to suspect the presence of sugar. In rare instances diabetic urine with sugar demonstrable may have a specific gravity of 1.015 or even lower. A specific gravity above 1.05 is rare. Naunyn has seen a case with 1.06. The highest specific gravity recorded was in 2 cases reported by Bouchardat and Prout, in each of which it was 1.074. Very high specific gravity—1.07 or over—always suggests fraud.

The most characteristic feature is the presence of sugar and the diagnosis is largely dependent upon this. This is almost invariably grape-sugar (glucose, dextrose). Normal urine contains glucose in quantities not demonstrable by the ordinary tests. In rare instances levulosuria may occur either with glucosuria or alone. Authentic cases have been reported by Seegen, Külz and May. Külz and Vogel have frequently noted pentosuria in human diabetes, and in experimental diabetes in animals, even after prolonged fasting, showing that the pentose originates in the animal body. The amount of sugar excreted varies considerably at different periods of the day. The period of minimum output is in the late night or early morning hours. According to Naunyn there are two periods of maximum output; one in the late morning hours, the other about six o'clock in the afternoon, occasionally lasting until midnight. The amount of sugar usually begins to increase about one and a half

to two hours after a meal. The percentage of sugar should be determined from a sample of urine taken from the mixed twenty-four-hour amount. Knowing the total amount of urine, it is then easy to calculate the total amount of sugar, in grams or grains, excreted daily. This is the only satisfactory way of following the progress from day to day or from week to week. Variations in the percentage of glucose excreted at different periods of the day are much less marked in the severe than in the mild cases, and in the former, the sugar of the night urine may exceed that of the day. In the latter, the variations are often quite marked and the urine of the early morning hours may be free from sugar. The percentage of glucose varies greatly. In the majority of cases it ranges about 3 per cent. In the severe cases it reaches 5 per cent. or over. It is very rare to meet with more than 8 or 9 per cent., although Naunyn reported a case with 11 per cent. and Higgins and Ogden a case of traumatic diabetes with 20 per cent. of glucose. The total output of sugar for the twenty-four hours may be only a few grams in the mild cases. In some cases the quantity of sugar may be enormous. It is not unusual to see cases with a daily excretion of 500 grams (15 ounces). Charcot reported a case with 1100 grams (35 ounces), Lecorhé a case with 1200 grams (38 ounces), and Dickinson a case cited by Naunyn with the enormous output of 1500 grams (48 ounces).

Many factors influence the sugar output. Diet is the most important one. Carbohydrates cause a marked increase, whereas a diet consisting exclusively of proteins and fat will cause the sugar to disappear in mild cases and will reduce it to a minimum in the severe cases. Acute febrile diseases and septic infections often cause a marked reduction. It is not unusual in diabetes with pulmonary tuberculosis accompanied by high fever, to see the sugar almost entirely disappear in the terminal stages. The onset of coma manifestations is not infrequently attended by a marked reduction in the sugar excretion.

The reader is referred to the works on Clinical Diagnosis for the methods of performing the various tests for glucose. Those generally used are the Fehling copper test (or one of its modifications) and the bismuth, fermentation, polariscope, and phenylhydrazin tests. Glucose reduces alkaline copper and bismuth solutions ferments with yeast, is dextrorotatory, and with phenylhydrazin produces an osazone, the crystals of which melt at 204° to 205° C.

Precautions to Observe in Performing the Sugar Tests.—It is a safe rule never to rely on one qualitative test alone. The most reliable single test is the fermentation test. If there is a rapid reduction of the copper sulphate in performing Fehling's test, one can be reasonably certain that the reducing agent is glucose. Where it is slow and slight, and, especially, if the precipitate be yellow rather than red, other reducing agents must be considered and eliminated. The other substances which reduce alkaline copper sulphate solutions are conjugated glycuronic acid, sometimes eliminated after the taking of certain drugs, alkapton (homogentisic acid), lactose, excess of uric acid, and kreatinin. The conjugate glycuronic acid also reduces bismuth, but is differentiated from glucose by being levorotatory as voided, becoming dextrorotatory

when the glycuronic acid is split off by boiling with an acid. It does not ferment. Alkaptonuric urine is recognized by being negative with the bismuth, fermentation, and polariscope tests. Its special feature is its darkening on exposure to the air and on the addition of an alkali. Lactose, which is very frequently eliminated in the urine in the early days of lactation, and when there is retention of the milk in the breasts either from obstruction of the milk-ducts or from sore nipples, reduces copper sulphate and bismuth, and is dextrorotatory, but does not ferment. Pentose reduces copper solutions only after considerable heating and then suddenly throughout the whole fluid. It yields a gray precipitate with Nylander's bismuth test; does not ferment; and may be dextrorotatory or inactive, depending upon the variety present. It gives the orcin test. Although excesses of uric acid and kreatinin may cause slight reductions of copper sulphate, there should be no difficulty in differentiating these from glucose if one takes the precaution to use one or more of the other tests, with which they are negative.

Other Urinary Ingredients in Diabetes.—Mayer has shown that *glycuronic acid*, like sugar, is present in normal urine in minute traces, and that it is increased in diabetes. It is regarded as one of the intermediary products of carbohydrate metabolism. It is recognized by the orcin test. Rosin and Alfthan demonstrated that the benzoyl esters are also increased. These normally do not exceed 2 to 3 grams daily. Edsall has found as high as 12.5 and 13.8 grams in 3 cases of diabetes.

Cambridge, by his so-called "pancreatic" reaction in the urine, which is dependent on some substance thought at first to be glycerin split off from fat in fat necrosis, claims to be able to determine what cases of diabetes are of pancreatic origin. He has now obtained a positive test in 121 of 168 cases of diabetes, or 72 per cent. A positive reaction is believed to indicate active degenerative changes of an inflammatory nature.

The urine of diabetics before and during coma symptoms very frequently, if not always, contains β -oxybutyric acid ($C_4H_8O_3$) and its derivatives, *diacetic acid* ($C_4H_6O_3$) and *acetone* (C_3H_6O). Acetone first makes its appearance, later diacetic acid, and still later in the severest cases, β -oxybutyric acid. In a diabetic case it is fully as important for the physician to test for these as for sugar. Their early recognition will aid in so directing the treatment that threatened coma may be warded off. It is not customary to test for *β -oxybutyric acid* as a routine owing to there being no simple, quick test. It is important to remember that it is levorotatory and may partly neutralize the dextrorotatory action of glucose. Diacetic acid and acetone, for which there are quick tests, should be tested for as a routine. Their presence in the urine always indicates that *β -oxybutyric acid* is being formed.

Diacetic acid is formed from *β -oxybutyric acid* by the latter taking on an atom of oxygen and splitting up into diacetic acid and water. It is recognized by Gerhardt's ferric chloride test.

Acetone, when present in large quantities, may give the urine a fruity odor. It may be recognized by Legal's sodium nitroprusside test, or by Lieben's iodoform test.

The *nitrogen* output is greatly increased, chiefly in the form of urea. This is due largely to the greater amount of proteins ingested, but also in part to increased destruction of the body proteins in the more severe cases. Pettenkofer and Voit have shown that, even when fasting, a diabetic patient excreted about 8 per cent. more urea than a healthy person. Leo has shown that the addition of carbohydrates to the diet of a diabetic will occasionally diminish nitrogenous metabolism.

An interesting feature is the extraordinary increase in the *ammonia* nitrogen output in the severe cases, particularly when coma supervenes. According to Neubauer, the average amount of ammonia nitrogen excreted in the urine by a normal individual on a mixed diet is about 0.7 gram daily. Part of the ammonia which should go to form urea is utilized in neutralizing the acids producing the acid intoxication. Naunyn reports having found an excretion of 5.8 grams of ammonia in a child weighing 48 pounds, and states that a daily excretion of 6 to 7 grams is not unusual in adult diabetics. Stadelmann records a case with an elimination of 11 grams. The amount of ammonia excretion can be taken as a safe measure of the grade of acid intoxication in diabetes.

The *uric acid* excretion is usually increased, as had been shown by Naunyn, Riess, and others. Gaethgens, in a diabetic with fever, found the uric acid excretion was 2.2 grams in the twenty-four hours. The increase is explained by the excessive proteins taken. It is very common to see diabetic urines with uric acid sediments. This precipitation is probably in part due to the diminished power of diabetic urine to retain uric acid in solution. Bischofswerder has shown that the total *alloxuric bodies* are also increased. Senator found the creatinin increased up to 2 grams daily. This is referable to the increased ingestion of meat and to the increased destruction of the muscular tissues of the body.

Oxaluria often occurs, with an actual increase in the excretion of calcium oxalate. Teubbaum has shown that the lime salts are markedly increased in severe cases of diabetes, but not in the mild. The *sodium chloride* is increased. The *sulphates* and *phosphates* are in excess, owing to the increased destruction of ingested and body protein, with oxidation of the sulphur and phosphorus of the protein molecule. A form of "phosphatic diabetes" has been described by Tessier, Ralfe, and others, due to an excessive excretion of calcium phosphate. There is nervous irritability, deranged digestion, emaciation, and pain in the back. In severe cases there may be polyuria, and the symptoms may simulate diabetes. The affection has really nothing to do with true diabetes, although it is said that traces of sugar have been found in some cases or have subsequently developed.

Albuminuria is absent in the majority of cases of diabetes when they are first admitted to a general hospital. In private practice with a larger proportion of mild diabetes in elderly persons, it is more common. Five groups of cases of albuminuria may be recognized: (1) Cases of severe diabetes of considerable duration, with traces of albumin, but no other evidence of actual nephritis. (2) Those in diabetics of advanced age, with indications of arterial changes. (3) Those in which, in addition to albuminuria, there are evidences of chronic nephritis, such as œdema,

headaches, albuminuric retinitis, and cardiovascular changes. (4) Cases of severe diabetes complicated by diabetic coma. When coma symptoms have definitely manifested themselves, albuminuria is practically always present. (5) Cases in which the albuminuria is due to a cystitis, or a balanitis in the male and vulvitis in the female. Naunyn and others state that diabetes mellitus occasionally passes over into a true nephritis, with disappearance of the glycosuria.

Casts are rare in diabetic urine except in those cases complicated by actual nephritis. There is one striking exception, however. Külz first pointed out that diabetic coma is accompanied by an abundant deposit of casts. A urine previously free from them and quite clear may suddenly become turbid, even on voiding, owing to the enormous number of casts present. In a very short time these settle to the very bottom of the glass as a grayish-white sediment. When pipetted off and examined microscopically, the field is found to be crowded with rather short hyaline and granular casts. The albuminuria and cylindruria of diabetic coma are probably evidences of a toxic nephritis. In cases of cystitis, balanitis, and vulvitis, pus cells will be found in the urinary sediment.

Diabetic urine, on standing, soon becomes turbid, owing to the growth of yeast cells. This fact is of practical importance, as it indicates that suspected urine should be examined qualitatively and quantitatively as soon as possible after being voided, particularly in warm weather. The yeast causes fermentation of the sugar, and when the glycosuria is slight, it may cause a complete disappearance of the glucose, and in all cases will cause a reduction in the percentage of sugar on quantitative determination. The presence of yeast cells in a urinary sediment should always arouse a suspicion of the existence of glucose. In balanitis in the male and vulvitis in the female, there is often a fungus growth in the inflamed mucous surfaces, and fungus spores and mycelia may be washed away in the urine during voiding.

Occasionally yeast cells and fungi develop in the bladder and set up fermentation processes, with the production of gas, *pneumaturia*. This is a rare condition. Leube found that diabetic urine contains a substance which gives all the reactions of *glycogen*. *Lipuria* has been described, the fat occurring in the form of a fine emulsion.

Complications.—1. The Skin.—*Boils* and *carbuncles* are very common, so much so that when they exist one immediately thinks of diabetes as a cause. Their frequency is due to the susceptibility of the tissues of the diabetic to infection. Boils are more common in the milder forms of the disease and in stout diabetics. Seegen says he has never seen boils in an advanced stage of the disease. The commonest seats are the neck, back, and buttocks. Cultures usually show staphylococci. Carbuncles are less common but more serious. They are more likely to occur in the severe cases and may precipitate coma.

Owing to the irritation of the genitals by the saccharine urine, and to the growth of fungi (hyphomycetes) in the superficial layers of the skin, inflammation of the prepuce and glans in the male, and vulvitis in the female, may occur. This may be attended by intolerable *pruritus pudendi*, particularly in women, in whom local boils or phlegmons of

the genitals may develop. The *general pruritus* of diabetes is due in all probability to irritation of the sensory nerves by the sugar in the blood, just as pruritus in jaundice and uremia is due to circulating toxins. *Urticaria*, *purpura simplex*, *purpura hemorrhagica*, *dermatitis herpetiformis*, *gangrena diabetica*, *bullosa serpiginosa* (Kaposi) may occur. (Edema of the feet, even without evident renal or cardiac affections, is not uncommon in advanced cachectic cases. A curious mottled cyanosis of the extremities is sometimes observed. In rare instances, the skin may be bronzed, constituting the so-called *diabète bronzé* cases. The pigmentation is a symptom of the disease known as hemochromatosis, in which glycosuria sometimes occurs in the late stages when the interstitial pancreatitis becomes marked. *Herpes zoster* and *perforating ulcer* of the foot occasionally occur, and are expressions of a diabetic neuritis. Sample and Gorham reported 7 cases of perforating ulcer among the first 275 diabetics admitted to the medical wards of the Johns Hopkins Hospital. A *paronychia diabetica* may occur. This may result in the loss of the nails. Williamson has observed 3 cases with bulbous fingers, due apparently to vasomotor changes. The writer has seen 3 cases of Dupuytren's contraction of the palmar fascia in three diabetic brothers.

Spontaneous diabetic gangrene occurs usually in diabetics after fifty. The glycosuria is usually of a mild grade. It is commonest in the lower extremities, and generally begins with a bluish discoloration and then a blackening of the skin of the big or little toe. It is of a moist type and may subside, but usually extends gradually to involve the whole foot or leg until stopped by amputation. It may start in the heel. William Hunt analyzed 64 cases. In 50 the distribution was as follows: feet and legs, 37; thigh and buttock, 2; nape of the neck, 2; external genitals, 1; lungs, 3; fingers, 3; back, 1; eyes, 1. The artery supplying the affected area shows arteriosclerosis in the vast majority of cases. In many instances it is thrombosed, and Naunyn states that he has never failed to find obliteration of the pulse in the early stages of the complication. Phlebitis, particularly of the veins of the leg, occasionally occurs. It was present in 1 case in the Johns Hopkins Hospital series.

Xanthoma diabeticorum occurs as a very rare complication. Up to 1892, Morris could find only 21 cases reported. The lesions consist of small nodules about the size of a pea, and having a yellowish or yellowish-red color. They are slightly sensitive and occur mainly on the buttocks, forearms, and knees. The eyelids are much less likely to be involved than in the xanthoma multiplex accompanying chronic jaundice. The xanthomata appear rapidly and disappear quickly with relief of the glycosuria by diabetic treatment. They may recur several times.

2. *Gastro-intestinal*.—An aphthous stomatitis due to the *oïdium albicans* occasionally occurs. At autopsy the pharynx and œsophagus often show a diffuse growth of this fungus. Gingivitis with pyorrhœa alveolaris frequently develops. The teeth decay rapidly and tend to loosen and fall out. The latter is probably due to a trophoneurosis. Gastrectasis occasionally results from the enormous quantities of food and liquids taken. There may be actual gastric catarrh. Although

moderate constipation is the rule, one occasionally meets with a case of obstinate diarrhœa. This is referable to an intestinal catarrh. Steatorrhœa, or fatty stools, may occur in pancreatic diabetes. Here fat digestion is interfered with, owing to changes in the pancreatic secretion, and the stools are of a pulpy consistence, of a dirty, dark-gray color, and of a greasy appearance. In these cases the movements are often very bulky, and at the end of defecation as much as a tablespoonful of almost pure fat may be passed. In a patient seen with A. D. Atkinson, of Baltimore, the autopsy revealed the presence of a large pancreatic calculus. Microscopically, large oil-globules and abundance of fatty acid and soap crystals are seen.

3. **Pulmonary.**—One of the commonest is *pulmonary tuberculosis*. Griesinger analyzed 250 cases of diabetes, and found pulmonary tuberculosis present in 42 per cent., and to be the cause of death in 39 per cent. In 50 autopsies, Frerichs found the lungs tuberculous in 25. In 149 of Naunyn's "pure" diabetic cases, it was present in 25, or 17 per cent., while in 113 cases, due to evident organic disease, there were 8, or 7 per cent. With the progress of the tuberculous process the glycosuria often diminishes, or may entirely disappear. Death may result from acute *pneumonia*, either lobar or lobular. A chronic interstitial pneumonia may occur. The pneumonia may be complicated by abscess of the lung. Gangrene of the lung is not very uncommon. Naunyn saw 12 cases, all of which terminated fatally with one exception. He describes three forms—an acute, a subacute or chronic, and a form with numerous gangrenous foci complicating a chronic pneumonic process, with fibrous induration.

4. **Heart and Arteries.**—Sufficient importance has not been attached to myocardial insufficiency in diabetes. It is not a rare occurrence. It occurs chiefly in the obese cases and in those with arteriosclerosis. The blood-pressure is usually moderately increased. The arterial changes may cause intermittent claudication, as was first pointed out by Charcot.

5. **Renal.**—These have been sufficiently discussed.

6. **Nervous System.**—Here only the nervous features directly referable to the diabetes will be considered.

(a) *Peripheral Neuritis.*—This is the commonest nerve complication. The numbness, tingling, cramps, and neuralgias are probably expressions of a mild neuritis. Sciatica is not uncommon, and other peripheral nerves, such as the inferior dental, may be affected. The neuritis may be multiple. Thus both ulnar nerves may be involved, causing muscular paralysis and anesthesia of the skin. As expressions of the neuritis, must be mentioned *falling out of the nails*, *glossy fingers*, *herpes zoster*, and *perforating ulcer of the foot*. The perforating ulcer closely resembles that of tabes. Williamson met 4 out of 140 cases. The sole of the foot, in the region of the metatarsophalangeal joint, is the commonest seat. The bone may be exposed or the joint opened. A corn may precede the ulcer. Attempts to remove the corn lead to infection, and the ulcer proceeds. On the other hand, trophic changes, due to the neuritis, constitute the chief etiological factor, and the ulcer may commence with superficial death of the skin. The ulceration is often painless.

As the knee-jerks are often absent, the lesion may be mistaken for the perforating ulcer of tabes unless the urine is examined.

A so-called *diabetic tabes*, resulting from a polyn neuritis, has been described. The pseudotabes closely resembles true tabes dorsalis, and was first described by Fischer, in 1886. It is characterized by lightning pains in the legs, loss of knee-jerks, and loss of power of the extensors of the feet. There is a characteristic *steppage* gait similar to that seen in arsenical, alcoholic, and in other forms of neuritic paralysis. A typical Argyll-Robertson pupil is rarely, if ever, present, although Charcot states that there may be atrophy of the optic nerve.

(b) A *diabetic paraplegia*, probably due to a peripheral neuritis, with paralysis of the arms and legs, has been described.

(c) Degeneration of the posterior columns has been described by Williamson, Sandmeyer, and Kalmus.

(d) *Hemiplegia* occasionally occurs. One would naturally expect to find some gross lesion to account for the paralysis, but cases have been reported in which careful search has failed to find any evidences of hemorrhage or thrombosis. The hemiplegia in these cases has been attributed to toxic causes, similar to the cases of hemiplegia in uremia without manifest brain lesions. Careful microscopic examination of the brain is necessary in these cases before stating that there is no organic lesion, and a thrombosed vessel may explain the complication.

In this connection the condition of the *tendon reflexes* may be considered. The knee-jerks are often absent, as first pointed out by Bouchard. Statistics differ as to the frequency with which the knee-jerks disappear. Gröbe found them absent in only 13.5 per cent. of his cases, whereas Williamson found them absent in 50 per cent. of his series. Their disappearance is probably dependent on a peripheral neuritis, or changes in the posterior columns of the cord. The Achilles reflex may disappear before the patellar, as in locomotor ataxia. The superficial reflexes—plantar, abdominal, and epigastric—are present in practically all cases. A patellar reflex may return after being lost. The condition of the reflexes bears no definite relationship to the prognosis, although the knee-jerks are more likely to be found absent in hospital than in private practice, the former cases being usually more severe than the latter.

(e) *Mental Complications*.—In addition to the psychical symptoms already described, a group of mental symptoms is occasionally met with closely resembling *general paresis*. Laudenheimer reviewed the relationship between diabetes and general paresis, and concludes that diabetes is not actually the cause of the latter. The mental symptom-complex is often improved under antidiabetic treatment. Actual general paresis is quite frequently the cause of glycosuria.

7. *Special Senses*.—Of the ocular complications, *cataract* is the commonest. Frerichs observed it in 19 cases out of 400 diabetics; Williamson, in 9 out of 100; and Seegen, in 4 per cent. of his cases. It occurs in the young as well as in the old. It is usually bilateral, and, in the young, of the soft variety, but in old diabetic patients, it is indistinguishable from the non-diabetic variety. There is no satisfactory explanation of its cause. The view that it is due to abstraction of water is no longer

generally supported. Diabetic retinitis occurs, but is not so common as albuminuric retinitis. Williamson found it in 7 cases among 100 diabetics, but in some of these, renal disease could not be excluded as a cause. It was first described by Jaeger in 1856. Hirschberg describes three types—a retinitis hemorrhagica diabetica, a retinitis centralis punctata, and a combined form. Rarely a *diabetic iritis* with hypopyon occurs. Diabetic amblyopia, due to a central scotoma, and *optic neuritis*, are rare complications. DeSchweinitz says that *premature presbyopia*, with failure to accommodate, is a common and often an early symptom. Sudden amaurosis similar to that in uremia may occur. The vitreous may contain masses of cholesterol crystals. Such a case has recently come under the writer's observation. Ear complications are not common. Furuncles in the external auditory meatus, and acute otitis media occasionally occur.

8. **Reproductive System.**—When diabetes develops during the child-bearing period, amenorrhœa usually results, and it is said that atrophy of the uterus may occur. Conception is rare. According to Gaudard, 33 per cent. of pregnant diabetic women abort. Herman states that premature delivery, due to intra-uterine death of the fetus, has occurred in about two-thirds of the published cases of pregnancy with diabetes. A diabetic mother may bear a healthy child, however, and has never been known to bear a diabetic one. Usually the diabetes becomes aggravated after delivery. Pregnancy may go to full term with marked amelioration or complete disappearance of the diabetic features. Herman favors early delivery, for the reason that the chances are two to one that the child will die *in utero*, and the earlier the pregnancy ends the more likely are the diabetic symptoms to ameliorate in the mother.

9. **Diabetic Coma.**—This is the most important and most serious of the complications of diabetes. Three types of coma occur:

(a) *Typical dyspnœic coma*, or Kussmaul's "air-hunger" type. This is the form that Kussmaul described, and is by far the most frequent of the three. As premonitory symptoms there may be lassitude, headache, epigastric pain, and occasional vomiting. The patient becomes restless and excited, and tosses about in bed. His speech becomes thick and eventually incoherent. He grows gradually duller, and eventually passes into deep coma. The pulse becomes small in volume, of low tension, and frequent, often reaching to between 120 and 140 per minute. A characteristic form of dyspnœa develops. It is inspiratory at first, but later expiration is also involved. When fully developed the respirations are full and voluminous; they are loud and can be heard a considerable distance, although they are not stertorous as in apoplexy; they are quite regular and are usually not increased in frequency. The volume of the chest is greatly increased with each inspiration, and it is this apparent demand of the system for air that led Kussmaul to designate the phenomenon as "air-hunger." The temperature is usually subnormal. There may be some cyanosis. The breath often has a fruity odor (owing to the exhalation of acetone), which may pervade the whole room. The urine may also have an acetone odor. Traces of albumin and enormous

numbers of short hyaline and granular casts occur in the urine just before and during the coma. Death almost invariably results, and occurs within forty-eight to seventy-two hours after the onset of the coma. Frerichs and others recognize also the two following forms:

(b) *The So-called Alcoholic Form.*—With headache and symptoms suggesting alcoholic intoxication; the speech becomes thick, the pulse rapid, and, without dyspnœa, coma supervenes and the patient soon dies.

(c) *The Diabetic Collapse.*—The patient suddenly begins to suffer from drowsiness and great weakness. The extremities become cold; the hands, feet, and face become livid; the pulse is small, thread-like, and 120 to 130 to the minute. The respirations are slightly quickened, but are shallow and not dyspnœic in character. Drowsiness develops, coma supervenes, and the patient dies in ten to twenty hours. There is no acetone odor to the breath nor acetone or diacetic acid in the urine. The collapse is believed to be due to cardiac failure, probably induced by myocardial changes.

Anomalous forms of coma occur, due to renal disease, cerebral tumor, meningitis, and apoplexy. The coma in these cases is due to the accompanying disease and not to the diabetes. The true diabetic coma of Kussmaul, or the "air-hunger" type, is by all means the most frequent and most important, and the following considerations mainly concern this form. A large percentage of deaths in diabetes are due to coma, and it is almost invariably the cause in children. An idea of its frequency can be gathered from the following statistics: Of Naunyn's 44 fatal cases, 19 died in coma, 12 of which were of the dyspnœic type. Frerichs reported 150 deaths from coma out of a total of 250 fatal cases; Taylor, 26 out of 43; Mackenzie, 19 out of 87; and Williamson, 28 out of 40.

Certain factors tend to predispose to the development of coma. Among these are constipation, excessive fatigue, the onset of various complications, such as carbuncle and pneumonia, subjection to an operation, and sudden changes in diet.

The complication is universally recognized now to be a manifestation of an acid auto-intoxication due to the abnormal circulation of β -oxybutyric acid in the blood. Previous to the establishment of this view, diabetic coma was attributed successively to the action of acetone and diacetic acid. Without qualification we can say that the intoxication of diabetic coma, or "acidosis," as Naunyn calls it, is due to the action of β -oxybutyric acid. By its action on the respiratory centre it causes the characteristic dyspnœa; and from its effect on the brain in general, coma supervenes. The β -oxybutyric acid is eliminated in the urine not as such, but in combination with the bases, chiefly as sodium oxybutyrate. In severe cases the output is enormous, reaching to between 100 and 200 grams daily, and in a case reported by Külz, to 225 grams. For a considerable time the available bases of the tissues (sodium, potassium, etc.) are sufficient to neutralize the acid; but when it is excreted for long periods these become used up, and then ammonia, derived from protein destruction, is called on for purposes of neutralization. This accounts for the enormous output of ammonia, reaching to 7 or 8 grams

in cases of threatened coma. The acetone excretion in the urine may reach 10 grams or more daily. That an acetonemia exists is indicated by the acetone odor of the breath in some cases. The presence of diacetic acid in the urine in the vast percentage of cases means that β -oxybutyric acid is also present. Acetone and diacetic acid are formed not alone from β -oxybutyric acid. This is indicated by their sometimes being present in the urine without the latter. It is now generally recognized that acetone is practically always formed from fat.

The presence of β -oxybutyric acid or diacetic acid in the urine should always serve as a danger-signal of approaching coma. There are exceptions to this rule, however, for one occasionally meets with cases in which a marked diacetic acid reaction persists for months or even years. Naunyn refers to a case in which there was an excretion of 100 grams of β -oxybutyric acid lasting for months, and of another diabetic in whom it had been detected for years. The source of the β -oxybutyric acid in the system has now been definitely settled. The β -oxybutyric acid and its two derivatives are produced as a result of the incomplete combustion of the fats of the body as well as those of the food. The latter suggests that it may also result from synthesis in the muscles or glands. It is particularly in the cases with this acid intoxication that we have the best proof that fat metabolism is also disturbed in this disease.

The relative amounts of acetone, diacetic acid and β -oxybutyric acid excreted may vary markedly in different stages of the disease. The first to appear is acetone, then diacetic acid, and lastly β -oxybutyric acid. In advanced stages of the disease, β -oxybutyric acid may be excreted in large amounts, acetone having practically disappeared from the urine. These changes are due to the gradual diminution of the powers of oxidation in the body. When it is possible to improve the body metabolism the acetone bodies disappear in the inverse order in which they make their appearance.

As a general rule, the addition of moderate amounts of carbohydrates to the diet causes a diminution in the excretion of acetone, as well as of the β -oxybutyric acid when it is present; their withdrawal causes an increase. While this is the rule in the mild cases, in the severest there are often exceptions. It seems to be quite certain that, when the capacity for oxidation in the body is not too much lowered, the presence of moderate amounts of carbohydrates in the food aids in the oxidation process and protects from destruction the fat which is believed to be the main source of the acetone bodies. The feeding of fats, however seems to be a frequent cause for an increase in these bodies, as has been shown by Schwartz and others. Joslin has demonstrated that the extent of acetone excretion depends on the capability of the fat for absorption, hence on the character of the fat employed. These considerations bear directly on the regulation of the diet when there are evidences of an acid intoxication.

With the development of coma manifestations and the appearance of β -oxybutyric acid in the urine, the sugar excretion often markedly diminishes, and the percentage of acid, which rarely reaches beyond 0.5 to 1 per cent., may exceed that of the sugar.

Course and Prognosis.—In children and very young individuals, diabetes runs a very rapid course, and almost invariably death is caused by coma. Cases are recorded by Benson, Becker, Bohn, and Wallach, in young individuals in whom the disease ran its entire course to a fatal termination within five weeks. Generally speaking, the later in life the symptoms first manifest themselves, the better the prognosis is. The majority of cases after middle life run a chronic course, and it is not very uncommon to see stout, elderly individuals in whom the disease has lasted ten to fifteen years. Joslin, in a recent analysis of his cases, has emphasized this point. Cases without hereditary influences are the most favorable. Once the disease is well-established, it is seldom, if ever, that a permanent cure is effected. Occasionally, however, one sees a glycosuria persisting for months or years in a very neurotic individual eventually entirely disappear. Naunyn cites cases of acute or subacute diabetes resulting from head-traumas in which there has been a permanent cure. The thought naturally arises, are these cases true diabetes, or are they instances of traumatic glycosuria? It is always well to determine the power of the individual to warehouse carbohydrates. If an individual on a non-carbohydrate diet excretes no sugar, the case may be considered a mild one. If, on the other hand, sugar is excreted, it means that it is being manufactured from the body-proteins, and the case is a severe one. The tolerance of a diabetic to carbohydrates is determined by ascertaining the number of grams of starch that can be added to the diet without sugar appearing in the urine. The presence of β -oxybutyric acid and diacetic acid in the urine is in the majority of instances of serious import, as they indicate the possibility of approaching coma. Once coma is well-established, a fatal termination almost invariably results, no matter how active the treatment may be.

Diagnosis.—There is usually no difficulty in arriving at a diagnosis if the precaution be taken to use two or three urinary tests, including fermentation, in any doubtful case. It is sometimes difficult to determine whether one is dealing with a true diabetes or a symptomatic glycosuria. This is the main factor in arriving at a decision in these instances. The presence of conjugate glycuronic acid compounds, homogentisic acid (alkaptonuria), pentose, levulose, lactose, excess of uric acid, or creatinin, may cause error in inexperienced hands. In a few of the cases of alkaptonuria the condition has been mistaken at first for diabetes. This was true in the case reported by the writer. The mistake is due to the fact that the homogentisic acid which is eliminated in the urine reduces alkaline copper sulphate solutions. The characteristic which the urine possesses of darkening on standing or on the addition of an alkali should arouse one's suspicions. Alkaptonuric urine, further, is negative with the bismuth, phenylhydrazin, fermentation, and polariscope tests. Bremer's blood-test may be of some value when a patient is seen for the first time with suspected coma symptoms and no urine is available.

Deception may be practised by the patient. Osler cites a case under his care of a young girl who had a urine with a specific gravity of 1.065, and in which the reactions proved to be those of cane-sugar. The

literature records 1 case in which a woman, after detection, bought cane-sugar and introduced it into her bladder.

Pentosuria, although only 19 cases have been recorded, is probably more common than is generally supposed. Some of the cases have been mistaken for diabetes. Salkowski and Jastrowitz reported the first case in 1892. The urine contained a copper-reducing substance which was optically inactive, did not ferment, and which from its osazone they identified as pentose. C. Janeway has recently reported 2 cases in brothers and states that there is a family predisposition to the disease. He describes three forms: (1) The alimentary pentosuria, due to the ingestion of large amounts of vegetables or fruits containing pentosanes; (2) rare cases occurring in severe diabetes in which the inability to burn carbohydrates extends to the pentose; (3) chronic pentosuria occurring without reference to the pentoses of the food. The sugar excreted in this form is the optically inactive *r*-arabinose. Pentosuria is recognized as follows: Fehling's solution is reduced in an atypical way, the color remaining unchanged for a minute or so after boiling, and then turning suddenly a green yellow or muddy orange color throughout. It gives the phenylhydrazin test, but is optically inactive and does not ferment. If doubt still remains the orcin test must be performed, in which the absorption bands of pentose are found with the spectro-scope.

Treatment.—Prophylactic measures should be taken in families in which there is a predisposition toward diabetes. Often there is also a tendency to obesity to these families. It is advisable to determine the ability of its individual members to warehouse carbohydrates. If glycosuria results from administering 100 grams of glucose on an empty stomach, it may be concluded that the assimilation for carbohydrates is lowered, for a normal person can take from 150 to 200 grams of glucose without sugar appearing in the urine. By restricting the carbohydrates in the members whose assimilation limit is shown to be lowered, von Noorden thinks that the possible development of diabetes in these individuals may be warded off.

It may be well to emphasize at this point that, although certain general principles govern the treatment of diabetes as a disease, yet it is the duty of the practitioner to study each individual case separately, with special reference to his dietetic needs. It is only in this way that the disease can be intelligently treated. The patient should be weighed periodically, say every two weeks in private practice and twice weekly in hospital work, and a careful record kept. The patient's weight is the best single criterion we possess of the success of any line of treatment. This has special reference to the dietetic treatment. No matter what the condition of the urine may be with reference to the presence or absence of sugar, the patient on any line of treatment must be regarded as doing badly if his weight is progressively diminishing. It is much better for the individual to excrete moderate amounts of sugar and hold or increase his weight than to be aglycosuric and steadily lose weight. It is important to keep this axiom always in mind, particularly in regulating the diet. It is not infrequent to find that a diabetic will lose weight

when on a non-carbohydrate diet and excreting no sugar or only small amounts, whereas he will begin to increase in weight if moderate amounts of carbohydrates be added, even though he excretes more sugar. This is probably explained by Leo's research in which he showed that the administration of a certain amount of carbohydrates to a diabetic spared protein metabolism.

Hygienic.—It is very important to look after the personal hygiene. Daily baths assist materially in keeping the skin functions active, and diminish the liability to furunculosis. By personal cleanliness the distressing pruritus can be partially alleviated. To the thin diabetic, with a dry, harsh skin, the luke-warm bath is often soothing. The more robust patients can stand a cold bath. An occasional Turkish bath is useful in the obese cases, as it is a partial substitute for massage. Light woollen underwear should be worn. Moderate exercise should be taken, as a certain amount of muscular activity favors sugar combustion. Violent physical exertion should be avoided in the severe cases, as it tends to induce coma. Massage is useful, as it tones up the muscular system and thus probably aids carbohydrate metabolism. All sources of worry and anxiety should be eliminated as much as possible. It is of the utmost importance that constipation should be corrected, as in severe cases it is held by many to favor the development of coma.

Dietetic.—We have seen that the symptoms of diabetes are directly or indirectly dependent upon the hyperglycemia, the grade of which is pretty accurately indicated by the amount of glucose excreted. Our object, therefore, should be to eliminate the hyperglycemia if possible. This will be most quickly effected by cutting out of the dietary those constituents that are most readily converted by the digestive processes into grape-sugar, namely, the carbohydrates.

When a diabetic patient comes under observation, the first duty is to ascertain the patient's capacity to warehouse carbohydrates, or, in other words, to determine his tolerance for carbohydrates. This is done by placing the individual for at least five days on a diet absolutely free from starches and sugar; that is, on a protein-fat diet. In so doing his weight must be taken into consideration and the diet so arranged that it will provide approximately forty calories for each kilo body weight. This can, as a rule, be fairly readily done—and in hospital work should always be done—as the protein and fat percentage of the various foods is given in some of the standard works on dietetics. Knowing that 1 gram each of protein and carbohydrate yields 4.1, and 1 gram of fat, 9.3 heat units, the caloric equivalent of the diet can be readily calculated. As the carbohydrates, which ordinarily provide the largest number of calories in our diet, are cut off, it will be seen that the proteins and fats must be largely increased to make up for this deficit. Before arranging the non-carbohydrate diet, the individual likes and dislikes of the patient should be ascertained, so as to secure one that will be most palatable and one that will likely be entirely eaten each day during the test. The following may be used as a "standard" diet for the tolerance test, subject, to be sure, to variations according to the patient's age, weight, and likes or dislikes for certain forms of meats:

Breakfast.—7.30 A.M., 120 grams (3iv) of beefsteak or mutton-chops without bone; two boiled or poached eggs; 200 cc. (3vj) of tea or coffee.

Lunch.—12.30 P.M., 200 grams (3vj) cold roast-beef, mutton, or chicken; 60 grams (3ij) celery, fresh cucumbers, or tomatoes, with 5 cc. (5j) vinegar, 10 cc. (5ij) oil, pepper, and salt to taste; 20 cc. (5v) whisky (if desired); 400 cc. (3xij) of water or Apollinaris water; 60 cc. (3ij) coffee.

Dinner.—6 P.M., 200 cc. (3vj) clear bouillon; 200 grams (3vj) roast beef; 60 grams (3ij) lettuce with 10 cc. (5ij) vinegar; 20 cc. (5iv) olive oil or three tablespoonfuls of some well-cooked green vegetable, as spinach; three sardines a l'huile; 20 cc. (5iv) cognac or whisky (if desired), with 400 cc. Apollinaris water.

Supper.—9 P.M., 2 eggs, raw or cooked; 400 cc. Apollinaris or Seltzer water.

With the four meals at least fifteen grams (about 3iv) of butter should be used in making the gravies and with the eggs. No milk or sugar is permitted with the tea or coffee. Saccharin may be used to sweeten them. The time of taking lunch and dinner, of course, may be reversed. This daily diet should provide a person of 60 kilos (132 pounds) with a little over the requisite 2400 calories for an individual of that weight. One precaution must be emphasized here. If the patient has been eating freely of starches these must be cut down slowly for two or three days before he is placed on the standard diet. Any sudden and radical change from one diet to another is liable to induce coma. It is well to keep the diabetic on the above diet for at least five days; by so doing it practically eliminates the possibility that any sugar excretion at the end of that time is derived from the stored-up glycogen of the liver.

While on this diet, the total amount of urine should be collected for each twenty-four hours, mixed, measured, and the sugar determinations made from a specimen of the twenty-four-hour amount. The reduction in the sugar excretion is often very striking in the first twenty-four hours. If the patient becomes aglycosuric within the first five days the case may then be considered a mild form of the disease, and it is then desirable to ascertain how much starch can be added to his diet without sugar appearing in the urine; in other words, to determine his tolerance for carbohydrates. This is probably best done by allowing the patient a weighed quantity of plain white bread, which contains approximately about 55 per cent. of starch. For the first day 15 grams of bread may be allowed. If sugar fails to appear in the urine another 15 grams (about half an ounce) may be added the next day and so on until glycosuria does develop.

If the patient continues to excrete sugar after being on the standard diet for five days, it indicates that he is suffering from a severe form of the disease. It further means that the tolerance for carbohydrates is entirely destroyed, and that the sugar eliminated in the urine is manufactured from his tissue-albumins. In the cases in which glycosuria persists after the patient has been on the non-carbohydrate diet for five days, Naunyn recommends that a "hunger-day" be instituted, during which time no food is taken for twenty-four hours, water being permitted. In a certain percentage of these cases the patients will become aglycosuric

as a result of the starvation-day. Naunyn's reason for establishing a hunger-day is to remove the hyperglycemia, even though it be for only twenty-four hours. By so doing he claims that the tolerance for starches is increased, and that it is then possible to give small quantities of starch without glycosuria occurring, and which, without the hunger-day, would not be warehoused. This increased tolerance is believed to be due to the tissues securing a temporary rest from sugar formation. The writer's experience with the hunger-day is that it is useless to advise it if the percentage of sugar is 0.5 or over, as when it is that high the sugar rarely entirely disappears. In the treatment of diabetes it is most advisable to put them on such a standard diet at least every three months in order that their tolerance for carbohydrates may be increased.

Before instituting a hunger-day it is best to at first try a pure "vegetable-day," cutting off all the animal proteins. It has been found that animal proteins are actual irritants to the sugar-forming apparatus. The vegetable proteins do not possess this action to the same extent. Von Noorden considers Klopfer's glidin to be the most serviceable of the vegetable proteins in these cases. It can be given up to 80 to 100 grams daily. By substituting these vegetable proteins the traces of sugar can often be eliminated.

The foods the diabetic should be warned against taking, excepting with the permission of the physician, are as follows: Bread of all sorts, wheat, rye, and brown; all farinaceous preparations such as rice, sago, tapioca, hominy, semolina, arrow-root, and vermicelli.

Thick soups are to be avoided. Among meats, liver is about the only form to be prohibited, owing to the glycogen it contains. For the same reason, oysters are sometimes prohibited.

All starchy vegetables: Potatoes, turnips, parsnips, squashes, vegetable marrow, beets, corn, peas, and artichokes.

Beverages: Beer; the sweet wines and sweet aerated drinks. These are excluded owing to the sugar, and not to the alcohol they contain.

Fruits: Grapes, dates, figs, currants, raisins, dried prunes and plums, and other dried fruits rich in sugar, should be forbidden. Certain fruits such as peaches, apricots, stewed green gooseberries, may be permitted in mild cases. Some authorities on this disease are inclined to be rather more lenient in regard to fruits. It is well to remember that levulose (fruit-sugar) has been shown to be tolerated better by the diabetic patient than any other form of sugar.

Sugar for sweetening purposes must be omitted. Without the physician's permission, milk must not be taken.

The following foods the diabetic may take unconditionally: Soups: Bouillon, ox-tail, and turtle; broths; soups with marrow and eggs permitted. Fresh meats: All the muscular parts of the ox, calf, sheep, pig, deer, wild and domestic birds—roast or boiled—warm or cold, in their own gravy or in a Mayonnaise sauce.

Internal parts of animals: Tongue, heart, brain, sweetbreads, kidneys, marrow-bones, served with non-farinaceous sauces.

Preserved meats: Dried or smoked meat, smoked or salt tongue, corned beef, American canned meats.

Fresh fish: Dried fish, salt or smoked fish such as codfish, haddock, herring, mackerel, flounder, salmon, sprats, eels, etc., tinned fish, such as sardines in oil, anchovies, etc.; caviar.

Eggs: Raw or cooked in any way, but without any admixture of flour.

Fresh vegetables: Green lettuce, cress, spinach, cucumbers, onions, asparagus, cauliflower, red and white cabbage, French beans. The vegetables, as far as they are suited to this method of preparation, are best cooked with meat or a solution of Liebig's Extract and salt, and cooked plentifully with butter. The addition of flour is not permissible.

Preserved vegetables: Tinned asparagus, French beans, pickled cucumbers, mixed pickles, sauerkraut, and olives.

Spices: Salt, white and black pepper, Cayenne pepper, curry, cinnamon, cloves, nutmeg, English mustard, and capers.

Cheese: Neufchâtel, Edam, Stracchino, old Camembert, Gorgonzola, and other fat and so-called cream cheeses. Pure cream is permissible up to 2 to 4 ounces daily.

Beverages: All kinds of natural and carbonated waters, either clear or with lemon juice, or with rum, whisky, cognac, and cherry brandy. Light Moselle or Rhine wines, claret, dry sherry, or Burgundy, in amounts prescribed by the physician. Coffee, black or with cream, without sugar but sweetened with saccharin if desired. Tea, clear or with cream or rum.

From this list it will be seen that the number of articles not containing starch the diabetic may choose from is quite extensive, and permits him to vary his dietary from time to time. In making up the "standard diet" certain of the articles in the above list may be substituted for some of those in the diet outlined.

Bread is the article of diet the cutting off of which the diabetic tolerates least well. Sooner or later a craving for it is inevitable. Various substitutes have from time to time been put on the market. The oldest of these and the one in most extensive use is *gluten bread* or biscuits made from gluten flour, first introduced by Bouchardat in 1841. It is prepared by washing away the starch from wheat flour. It is easy to demonstrate that these gluten flours almost without exception contain starch. The profession and the public are too often imposed upon by some of the manufacturers of these gluten flours. The Pure Food Laws should demand that all these preparations state the carbohydrate content as well as that of the gluten.

Another substitute is bread or biscuits made from *aleurone flour*, advocated by Ebstein and prepared by Dr. Hundhausen of Hamm, Westphalia, Germany. It is a vegetable albumin prepared by a special process from wheat. It contains from 80 to 90 per cent. of albumin in the dry substance and only 7 per cent. of carbohydrates. In making bread from it, a considerable percentage of starch has to be added.

Flours prepared from the soya bean, almonds, cocoanuts, and Iceland moss, have had their advocates as substitutes for wheat flour. The writer's experience has been limited to the use of gluten and aleurone bread, and it has taught him that patients eventually tire of them and they still crave white wheat bread. Owing to the expense and the unreli-

ability of most gluten flours, the writer has given up their use. It is much better to allow a diabetic to have daily a definite weighed quantity of white bread, the starch percentage of which he knows to be about 55 per cent. Graham bread may be used as a substitute with advantage. Having ascertained the tolerance of the patient for white wheat bread, the equivalents in other carbohydrates of the patient for white wheat the equivalents in other carbohydrates may be substituted. These are often more bulky and more satisfying to the individual. These equivalents can be found in books on dietetics.

Starch, in the form of potato, is thought to be more easily assimilated than wheat starch, and the comparatively recent work of Mossé seems to bear this out. The observations at the Johns Hopkins Hospital tend to confirm this view. Mossé allowed his cases 1 to 1.5 kilos (2 to 3 pounds) of potatoes daily. He says that there is a marked amelioration of all the distressing symptoms under the potato treatment. It is best to bake the potatoes. Naunyn does not speak very enthusiastically of this special cure in his last edition. He thinks that when benefits result, it is due mainly to the fact that the diet in the case heretofore has not been properly arranged so far as the allowance of carbohydrates is concerned. Von Noorden recently has advocated very strongly a specially prepared oatmeal, and has claimed remarkable results in eliminating the glycosuria as well as clearing up the signs of acidosis.

In the mild cases of diabetes (those that have become aglycosuric on the standard diet), the best course to pursue is to add to this standard diet weighed quantities of white bread, the amount to vary with the tolerance of the individual. Occasionally, a baked potato may be substituted for the bread. In these cases milk is especially useful as it contains only between 4 and 5 per cent. of lactose which is very well assimilated by diabetics. A pint or a pint and a half, accordingly, may be permitted daily. The monotony of the standard diet may be from time to time relieved by taking substitutes from the list of unconditionally allowable foods given above.

In the severe cases (those who fail to become aglycosuric on the standard diet), at first thought it would appear that the addition of carbohydrates would be contra-indicated, as they would tend to increase the glycosuria, considering that the tolerance is *nil*. Experience, however, shows that these do better, and are more likely to hold their weight if given very moderate quantities of starchy food. The danger of coma is increased by any long continuation of an exclusive protein-fat diet. In both forms, a return to the strict diet, in order to increase the tolerance, should be made at least every three months, for a period of ten days. It is desirable at shorter intervals in the severe forms.

No attempt should be made to restrict the water taken by the diabetic. No good will follow by doing so, as the thirst and polyuria are dependent on the hyperglycemia. Harm, on the other hand, is likely to ensue, as the increased thirst causes mental and physical distress. Apollinaris and Seltzer water may be allowed, and the thirst may be quenched by drinking lemonade sweetened with saccharin instead of sugar. A drink made by dissolving a dram of cream of tartar in a pint of boiling water

and flavoring with lemon-peel and saccharin and then cooling, may be given freely for the same purpose.

Alcohol, in the form of whisky, cognac, or rum, is to be recommended as it aids fat digestion, and tends to make up for the loss in heat units resulting from the cutting off of carbohydrates. One gram of alcohol by its combustion yields 7 calories.

Sawyer, of Cleveland, claims to have obtained marked benefit in diabetes by systematic gastric lavage. Beveridge, of New York, has recently advocated the view that diabetes is due to intestinal auto-intoxication and has recommended the use of the "cure-all," the *Bacillus bulgaricus*. His views require further confirmation.

Medicinal.—Few diseases have had a greater number of drugs advocated for their treatment; all of which goes to show that most of them are useless. In connection with no disease is quackery in and out of the profession more rampant. It is the duty of the practitioner to discourage the patient from using proprietary remedies. These are all expensive and for the most part absolutely useless.

Only a few drugs have proved of any service whatever. The most useful is *opium* and some of its alkaloids. It is claimed that it diminishes the thirst, appetite, amount of urine, excretion of sugar, and nervous irritability. As a consequence, the weight increases and the general condition of the patient improves. Diabetic patients are unusually tolerant to opium and its alkaloids, and can take large doses without narcotism. By some, the crude opium, or the dried extract, is thought to give the best results. The patient may be started on half a grain (0.032 gm.) of either, three times a day, and this may be increased until a total of from 4 to 6 grains (0.25 to 0.4 gm.) daily are taken. Morphia in increasing doses has its advocates but the alkaloid now most extensively used is codeia. Von Noorden prefers the new opium derivative pantopon. Half-grain doses (0.032 gm.) of codeia sulphate after each meal may be administered at first, and increased until a total of 6 to 8 grains (0.4 to 0.5 gm.) daily is reached. It is less constipating than the crude drug or morphia. There should be a gradual withdrawal of the opiates when the sugar is reduced to a minimum.

Arsenic stands next to opium in its apparent efficacy. It may be given as Fowler's solution, commencing with 3 minims and gradually increasing up to 10, three times daily. In diabetes with marked functional nervous manifestations, bromide of potassium or soda is often useful. It tends to allay the nervous irritability and to diminish the glycosuria. It is probable that all these sedatives exert their effect through the chromaffin system by cutting off the impulses passing to it by way of the sympathetic nerves. The coal-tar products have been strongly advocated, and in neurotic cases antipyrine in 5- or 10-grain (0.3 to 0.6 gm.) doses, three times a day, may prove useful. Potassium iodide should be given a thorough trial where strong suspicions of a luetic basis for the disease exist. Salicylates may be given when there are evidences of rheumatic arthritis. Uranium nitrate in recent years has been strongly advocated in certain quarters, but is uncertain in its effects. Drugs play a very minor part in the treatment of diabetes. The writer rarely

resorts to them, excepting for the relief of special symptoms or complications.

Throughout the treatment, the urine should be regularly tested for the iron-chloride reaction for diacetic acid. If this be present, sodium bicarbonate in 2- to 4-gram (30 to 60 grain) doses, three times daily, should be administered. In this way the danger of coma may be averted.

Here, also, brief reference to treatment at *mineral spas*, and by alkaline mineral waters, may be made. Of the spas abroad, those of Carlsbad, Neuenahr, Vichy, Marienbad, and Contréxeville are probably the best for mild diabetics and particularly for those in whom there are gouty manifestations. No severe case should be recommended to run the risks of a long, fatiguing journey to reach these places. Only too often a fatal termination is hastened. Undoubtedly, many mild cases are benefited. How much benefit is actually attributable to the waters themselves is difficult to determine. Undoubtedly, those that are mildly laxative, and those containing considerable quantities of carbonates and bicarbonates, thus tending to neutralize the abnormal acids of the blood, are helpful. There is no question, however, that the chief benefit is derived from the greater willingness of the patient to submit to a dietetic regimen, and from the diversion and the freedom from business cares and worries. A bottle of Vichy or a couple of glasses of Carlsbad water daily may be taken with benefit in any part of the world. In the United States, mild cases may be benefited by a course at Saratoga Springs, where the Hawthorn water is probably the best, at Bedford Springs, Pennsylvania, and possibly, at Poland Springs.

Pancreatic preparations have been given a fair trial, but the results have been disappointing. This must necessarily be the case until we possess some clinical test by which we can recognize the cases due to pancreatic disease. Cammidge thinks this may be possible by his recently devised test. Pancreatic juice and extract have failed to produce any material benefit. Williams, of Bristol, transplanted the pancreatic gland of a sheep under the skin of the breast and abdomen of a diabetic. The patient died in three days of coma. Pancreon, with sodium carbonate, sometimes produces remarkable results in those cases of true pancreatic diabetes, characterized by enormous stools with abundance of undigested fat. Fat digestion is at once improved and there is often a prompt increase in body weight.

Treatment of Complications.—1. *Diabetic Coma.*—Certain factors predisposing to coma must be carefully guarded against. Obstinate constipation must be counteracted; prolonged restriction of a severe case to a diet entirely free from carbohydrates may tend to induce the complication. Sudden and radical changes from a mixed diet containing considerable starch, to a rigid diet, or *vice versa*, may precipitate it. We have seen that the coma is due to an acid-intoxication, the toxic agent being β -oxybutyric acid, derivative products of which are acetone and diacetic acid. The existence of an "acidosis," indicated by the elimination of either β -oxybutyric acid in the urine, or its product (diacetic acid), or an excess of ammonia, should at once be followed by the administration of sodium carbonate or sodium bicarbonate by

mouth. The most serviceable clinical test for the "acidosis" is the ferric-chloride reaction for diacetic acid. If this be present, sodium bicarbonate, in 2- to 3-gram (30 to 45 grain) doses, three times a day, should be started at once. The alkali neutralizes the acid in the circulating blood, and the tissue-bases (sodium, potassium, etc.), and the ammonia which is derived from the breaking down of the body-proteins are spared. In mild cases of acidosis, it is important to remember that the latter may be relieved by making moderate additions of carbohydrates to the diet if the latter has previously been very restricted. Naunyn states that when the ammonia excretion reaches 4 grams daily, he has never seen a case in which it was possible to ward off an attack of fatal coma.

When actual symptoms of coma have set in, treatment is almost hopeless, and the rule that prevention is better than cure is nowhere better illustrated than in this dreaded complication. When coma symptoms do intervene, the most active treatment should be instituted, however. Carbohydrates should be added to the food if the patient is still able to swallow. The knowledge that the administration of carbohydrates will diminish or clear up the acidosis when it has not reached too severe a grade is one of the important recent advances in the therapy of diabetes. The administered carbohydrate in some peculiar manner favors the more complete oxidation of the fats. In the severest cases of diabetes, even those with coma manifestations, the organism never entirely loses its capacity to burn up carbohydrates. Milk is most valuable in these cases. From 500 to 1000 cc. may be given in the twenty-four hours. Of all carbohydrates levulose is most easily burnt up by the diabetic. Recently von Noorden has advocated the subcutaneous injections of 5 to 10 per cent. solutions of levulose in cases with threatened coma. Naunyn prefers its administration either by mouth or by enema. It may be given up to a total of 100 grams (or over 3 ounces) daily. Realizing the origin of the acetone bodies, the importance of cutting down the fats in threatened coma becomes at once apparent. Those containing the lower fatty acids are most injurious. The fats permitted should be chiefly those of vegetables and meats, as these contain comparatively little of the lower fatty acids. Butter, if used, must be given in limited quantities and only after having been thoroughly washed with water to remove the above acids. It is probably better to entirely exclude butter in the threatened coma cases, as it has been shown to very materially increase the output of the β -oxybutyric acid. Sodium carbonate, or bicarbonate, should be given by mouth, rectum, and intravenously, in enormous quantities. As much as 4 to 8 grams (1 to 2 drams) of sodium bicarbonate, every hour, by mouth, if deglutition is still possible, and double this quantity per rectum every two hours, should be administered. More effectual results will follow an intravenous alkaline injection. Enormous quantities of sodium carbonate have been introduced at one injection. Thus Minkowski gave 84; Lepine, 44; Wolfe, 30, and Rosenstein, 20 grams at one operation. The temporary results are often striking. The respirations become quieter, and when the coma is not deep there may be temporary return to consciousness. As strong a solution of

sodium carbonate as 3 to 5 per cent. has been used. In practically all these cases there is a recurrence of the coma in a few hours and death within twenty-four or forty-six. The custom at the Johns Hopkins Hospital has been to introduce a liter of a 2 per cent. solution of sodium bicarbonate in normal salt solution slowly into one of the median basilic veins, and to repeat the procedure on the opposite side in four to six hours. From 200 to 400 cc. of blood should be first removed. Intravenous injections of Ringer's solution have been recommended. Naunyn states that once coma is well established he does not think it possible permanently to relieve it. The grade of the acid-intoxication in these severe cases is indicated by the fact that no matter how vigorously the alkalis are pushed, it is not possible to render the urine alkaline. Grünberger found acetone and diacetic acid in the cerebrospinal fluid, although the urine was free from diacetic acid. Naunyn suggests that in these cases there may be a direct toxic action on the central nervous system.

2. *Pruritus*.—Frequent bathing of the genitalia, to prevent them from becoming saturated with the saccharine urine, is the best preventive. Bathing with soda solution, or a weak solution of carbolic acid, may give some relief. The best remedy is a solution of boric acid or of hyposulphite of soda (30 grams or 1 ounce to the liter or quart of water), applied as a lotion. Ichthyol and lanolin ointment may give relief in some cases. Menthol ointment (grs. x to vaseline 3j) sometimes gives relief. These are purely local measures and the symptom will yield when the glycosuria is relieved by the usual measures.

3. *Gangrene and Carbuncle*.—As temporary measures, the affected parts should be dressed with bichloride compresses. Early amputation and excision, respectively, are indicated. There is a certain risk of either the anesthetic or the operation itself precipitating coma, but this is much less than the danger from the complications, as both are liable in themselves to cause death by inducing coma.

DIABETES INSIPIDUS

Definition.—A chronic affection, characterized by the passage of large quantities of pale urine of low specific gravity, free from sugar, albumin, and casts, and usually accompanied by an insatiable thirst.

Incidence.—Diabetes insipidus is a rare disease. There were only 8 cases among the first 106,000 patients admitted to the medical wards and dispensary of the Johns Hopkins Hospital. Among 113,600 patients treated at the Charité, Berlin, from 1877 to 1896, there were 55 cases, or 0.048 per cent. Eichorst observed 7 cases, or 0.02 per cent., among a total of 35,942 patients at the Zürich Hospital.

Clinical Classification.—The cases may be divided into two groups: (1) The primary or idiopathic cases. This group includes the hereditary cases in which it would appear that there must be a constitutional defect probably in the kidneys. It also includes all those cases in which there is no demonstrable organic basis for the disease. (2) The secondary or symptomatic cases. These include the cases in which there is evidence

of organic disease of the central nervous system or elsewhere, the lesion being responsible for the symptoms.

Another classification is as follows: (1) Those cases in which there is an organic basis for the disease in the central nervous system; (2) those in which a functional neurosis coexists; and (3) the renal type.

Etiology.—The majority of cases occur in comparatively *young persons*. Of 85 cases collected by Strauss, 9 were under five years, 12 between five and ten years, 36 between ten and twenty-five years. In van der Heijden's series of 87 collected cases, there were 7 in the first, 19 in the second, 23 in the third, and 19 in the fourth decade. An *hereditary tendency* has been noted in certain cases. The most remarkable instance of the influence of heredity is in the family reported by A. Weil. Of 91 members of four generations, 23 had persistent polyuria without any deterioration of health, namely, the great-grandfather, his three children, seven grandchildren, and twelve great-grandchildren. Of the 22 affected descendants of the original case, there were 11 males and 11 females. The cases were congenital and persisted throughout life. Lacombe, Pain, and Gee, have reported similar instances of heredity in this disease. Males are more liable to the affection than females. Cases have been reported to be due to the effects of exposure, drinking copiously of cold fluids, and a drinking bout. Trousseau noted that it was not unusual to find that the parents of patients suffering from diabetes insipidus were either albuminuric or glycosuric. Ralfe emphasized the frequency with which a history of tuberculosis, syphilis, and gout, were obtained in one or both parents.

In the last few years the *kidneys* and *pituitary gland* have been the two organs that have been especially studied, with the view of finding a cause for the disease. From the work of Tallquist and Eric Meyer, it is now generally held that the renal type of the disease is due to the incapacity of the kidneys to secrete a concentrated urine. This loss of power applies chiefly to the salt and urea. Here the polyuria is primary. Forschbach has recently reported these findings. On the other hand, it has been shown that when the disease is part of a functional neurosis there is no disturbance in the secretory action of the kidneys, and polydipsia is the primary symptoms. In the group, dependent upon an organic disease of the nervous system, lack of power of concentration of the urine has been found when the kidneys have been tested.

Our knowledge of a possible relationship between the *pituitary gland* and diuresis dates from 1901 when Schaefer and Magnus discovered that extracts of the posterior lobe of the hypophysis possess diuretic properties of a high degree. Clinically, E. Frank, Hagenback, Rosenhauf, Oppenheim, and Finkelnburg have reported cases where there have been tumors, gunshot wounds, or cysts involving the pituitary with a resultant diabetes insipidus. Cushing and his associates have brought forward the most convincing evidence yet published of the potency of lesions of the pituitary in producing an extraordinary polyuria, as, for example, following manipulation of the posterior lobe or its removal in dogs. He reports a case with a urinary output of 10 to 12 liters in a man twenty-two years of age, in whom at autopsy there was a

lymphosarcoma of the cervical glands and an infiltrating growth occupying the thickened stalk of the pituitary. Another most instructive case was a woman who was totally blind, who developed a polyuria of 12 liters following manipulation of the pituitary in an inoperable tumor. The thirst was simply insatiable in this case. In an analysis of his series of 100 cases of primary hypophysial disease 6 showed so marked a polyuria that a diagnosis of diabetes insipidus was justified and in 5, such a diagnosis had actually been made by the physicians previously attending the cases.

Another important contribution made by Cushing, Weed, and Jacobson occurred during their study of the autonomic control of the gland. They found that the nervous impulses from the medulla pass through the cord to the three upper dorsal nerves and thence to the pituitary gland by way of the cervical sympathetic. Stimuli applied to this pathway cause a glycosuria and also a marked temporary polyuria, the urine being of a low specific gravity. They hold that these observations are of importance in connection with the etiology of emotional and neurogenic polyurias.

The writer has been impressed with the importance of *cerebral syphilis* as a cause of the affection, having reported 9 cases of diabetes insipidus, in 4 of which, from the history, symptoms, and the improvement under potassium iodide, it seemed without doubt that cerebral syphilis was the cause. In 1 of these the lesion was a gumma, and in the other 3 the symptoms pointed toward there being a basilar syphilitic meningitis as a part of the syphilitic lesion. Polyuria and polydipsia have long been described as symptoms of cerebral syphilis. Fournier reported 6 cases in which these symptoms were present in association with various cerebral manifestations of the disease. The lesion usually producing the polyuria is a basilar syphilitic meningitis. This was the form of lues in Buttersack's case, in which the disease was localized mainly in the interpeduncular space. Polyuria was the initial symptom in his patient. Nonne states that it is not necessary, as was formerly held, that the lesion should involve the medulla oblongata or its vicinity. He asserts that all we can say is that polyuria and polydipsia are most liable to occur in syphilitic brain lesions which manifest themselves in the form of a diffuse basilar meningitis. One can appreciate how a basilar meningitis might cause a polyuria when one recalls that in experimental polyuria it has been shown that injuries to the middle lobe of the cerebellum and to the superficial areas of the pons and medulla caused a profuse flow of urine.

Many of the cases of diabetes insipidus due to basilar syphilitic meningitis have been associated with a peculiar form of bilateral hemianopsia. Oppenheim considers an "oscillatory" form of hemianopsia or "hemianopsia bitemporalis fugax" as being practically pathognomonic of this particular lesion. He has reported 3 such cases, in 1 of which polyuria and polydipsia were associated. Spanbock and Steinhaus state that in 50 collected cases of temporal hemianopsia there was polyuria in 11. The hemianopsia comes and goes several times in the twenty-four hours, and such a history was obtained in 2 of the 4 cases of diabetes insipidus

with cerebral lues reported by the writer. Hemianopsia is also a very common neighborhood symptom of pituitary tumors.

The recent demonstration that manipulation or tumors of the pituitary can produce polyuria affords a possible explanation of the occurrence of diabetes insipidus in the cases of basilar syphilitic meningitis. The meningeal process is often most marked in the interpeduncular space, and it is easy to conceive that hyperplastic changes with consequent oversecretion of the posterior lobe of the pituitary could be produced.

Hadra and Ralfe have reported cases accompanying aneurysm of the carotid and the abdominal aorta respectively. The disease has not infrequently been noted in affections of the abdominal viscera. In 1794, Frank observed a fatal case in a patient with chronic disease of the intestine. Schapiro reported 5 similar cases from Eichwald's clinic. Dickinson recorded an instance in a patient with carcinoma of the liver with secondary metastases in the retroperitoneal lymph glands, which had involved branches of the solar plexus.

Affections of the spinal cord have, in rare instances, been regarded as the cause of the disease. Schlesinger saw a case in a patient with tabes. In a case of Westphal's, it occurred in association with spastic spinal paralysis. F. Schultze saw a case in a patient with a diffuse tumor of the cord. Instances of persistent polyuria have been observed by Krause in syringomyelia, and by Friedreich in hereditary ataxia.

Diabetes insipidus has followed the infectious fevers, for example, after typhoid, typhus, diphtheria, measles, and scarlet fever.

In very rare instances, a diabetes mellitus may pass over into a diabetes insipidus. This is most likely to occur after traumatism of the brain, in which, at first, sugar accompanies the polyuria, but later disappears leaving the characteristic urinary features of diabetes insipidus. Occasionally, however, diabetes insipidus may pass over into diabetes mellitus. In 1897, Senator reported such a case in a woman, aged forty-three years, who, since childhood, had voided daily from 12 to 15 liters of urine of a specific gravity of from 1.001, to 1.003, and who developed a mild glycosuria. Three years before her death 0.3 per cent. of sugar was found in her urine. No organic lesions were detected at autopsy.

Theories as to Cause.—The essential cause for the polyuria has been the subject of much research, and is still far from being satisfactorily explained. Dietrich Gerhardt states that in the idiopathic forms "the disease is due to a disturbance of the secretory function of the kidneys and not to an increase in the thirst or to blood changes." Eric Meyer, in a research from Müller's clinic in 1905, comes to the conclusion that in diabetes insipidus one has to do with a primary polyuria which results from an incapacity of the kidneys to secrete a urine of normal concentration. In consequence of this functional incapacity of the kidneys, the diabetes insipidus patient, in order to eliminate the end-products of tissue metabolism circulating in the blood, has to imbibe larger quantities of water than does the normal individual. Thus, the administration of sodium chloride to a patient with primary polyuria is not followed by the elimination of a urine of increased specific gravity, the quantity of urine being actually increased. In primary polydipsia, on

the other hand, according to Meyer, the power of the kidneys to secrete a more concentrated urine is not destroyed. Thus, the administration of sodium chloride to such a patient is followed by an increase in the specific gravity, without any increase in the volume of the urine.

In the cases with organic lesions of the brain it now seems probable that in the majority of them the polyuria is due to an increase in the secretion of the posterior lobe of the pituitary, which is known to have a powerful diuretic action. In those in whom a functional neurosis exists it is quite possible that this secretion also is increased, since the gland receives its nerve supply from the cervical sympathetic.

Morbid Anatomy—There are no lesions peculiar to the disease. The various morbid processes found at autopsy are primary rather than secondary. The kidneys are usually enlarged and hyperemic. The bladder is dilated, and its walls hypertrophied. Dilatation of the ureter and pelves of the kidneys is occasionally found.

Symptoms.—The disease may begin abruptly, as after a severe fright. More commonly it develops slowly. Polyuria is the most constant and characteristic feature. The quantity of urine passed daily may be enormous. Trousseau had a patient, aged twenty-four years, who passed 43 liters in a day. The weight of the urine voided daily may almost equal that of the patient. Thus, Vierordt cites an instance of a child weighing 13.2 kilograms, voiding 12.3 kilograms of urine daily. The largest daily elimination in any of the writer's 9 cases was 16.5 liters. One passed 1700 cc. at a single voiding. The urine is usually almost colorless, but may have a bluish tint. The specific gravity generally ranges between 1.001 and 1.005. The urine is usually free from albumin, sugar, or casts. Occasionally, traces of albumin appear in the late stages. In the early stages the output of urine may far exceed the intake of fluids. This is due to withdrawal of fluids from the tissues. The writer has noted this inequality in cases of long standing. Dickinson conducted experiments suggesting that this was in part due to absorption of the moisture of the air through the skin. The balance of opinion favors the view that a condition of "bradyuria" rather than "tachyuria" exists in this disease. In other words, when a copious draft of fluid is taken, an increase in the flow of urine is slower in making its appearance, and the total elimination is slower in a patient with diabetes insipidus than in a healthy individual. Muscle-sugar, or inosite, has been frequently demonstrated in the urine. This is believed to result from the flushing out of the muscles by the enormous quantity of fluids.

Thirst is practically a constant and often a distressing symptom. In many cases it is the first one complained of, as it first attracts the patient's attention. One patient of the writer said he "simply lived to drink," and described the infinite satisfaction it gave him to be able to take a whole pitcher of water at one draught. Trousseau's patient drank 50 liters in twenty-four hours. In experiments in which the fluids have been cut off, the patient, as in Strubell's case, has been known to drink his own urine. It is very difficult in many cases to determine, from the history or otherwise, whether one is dealing with a primary polyuria or a primary polydipsia. These can scarcely be considered independent

diseases however. Nothnagel's case is usually cited as a typical instance of a primary polydipsia. A man, aged thirty-five, was kicked in the abdomen and fell, striking his head, in the region of the right ear, against a stick of wood, but was not rendered unconscious. Half an hour later he began to have intense thirst and drank three liters of water, but it was not until about three hours afterward that the first urine was voided. Buttersack gives the following conditions as indicating a primary polydipsia in any particular case: (1) There is normal sweat secretion. (2) The urine is less than the amount of fluids taken. (3) The polyuria ceases on cutting off the fluids. (4) The urine elimination and liquids taken run parallel. Stoermer states that in primary polydipsia the blood is of normal concentration, while in primary polyuria it is increased.

The appetite varies considerably; often it is not increased, and may be diminished. On the other hand, it may be ravenous, as in Trousseau's patient, who ate in the Paris restaurants, where the meals were at a fixed price and the bread was not charged for. He devoured so much of the latter that it was more profitable for the restaurant keepers to pay him to remain away. These bulimia cases are the ones in which there is such a marked increase in the urea output. Absence of sweating is the rule; the insensible perspiration is also diminished. Constipation is common. Cataract has been described. One of the writer's patients has bilateral plaques of xanthoma palpebrarum. As already stated, there may be recurring attacks of transitory bitemporal hemianopsia in cases due to basilar syphilitic meningitis. Choked disk may be present. Paralysis of the sixth nerve is sometimes seen. Many of the cases due to cerebral disease have intense headaches. Some suffer early and throughout the disease, with racking pains in the back and legs. In one of the writer's cases there were several attacks of transitory left-sided hemiplegia, followed by an attack of longer duration, from which it took weeks to recover. Impotence not infrequently occurs. Marked emaciation may develop in the secondary symptomatic cases. In the idiopathic cases, on the other hand, there may be no loss in weight. Edema of the feet may occur in the last stages of the asthenic cases. In contrast to diabetes mellitus, the knee-jerks are likely to be exaggerated. Of 9 cases, they were exaggerated in 5, normal in 1, diminished in 2, and not noted in 1. The results of researches show that metabolism is but little disturbed, notwithstanding the abnormal fluid exchange. In some of the cases the blood is concentrated and the red cells may be between six and seven millions per cmm. The temperature is always subnormal, unless some complication intervenes. During febrile attacks the amount of urine may diminish considerably. The pulse is usually of small volume, and there is said to be no increase in the blood pressure. Toward the end the exhaustion may be extreme. Death is sometimes preceded by an uncontrollable diarrhœa. Drowsiness eventually ensues, and death occurs with the patient in coma. The immediate cause in many cases is a low form of congestive pneumonia.

Diagnosis.—There is no arbitrary line separating the physiological from the pathological polyurias, so far as the amount of urine is concerned. The chief distinguishing features of the polyuria of diabetes

insipidus is its permanence, a physiological polyuria usually being transitory. The greatest difficulty will arise in distinguishing the cases from those of chronic interstitial nephritis, where an abundant, pale urine is common. In the latter, the existence of albumin and a few casts, with certain cardiovascular features, should prevent much difficulty. The hysterical polyuria will usually be recognized by the existence of certain nervous and psychical symptoms. The polyuria, further, is likely to be intermittent in character. Some have included hysterical polyuria as a form of diabetes insipidus, but this hardly seems justifiable. The absence of sugar and the low specific gravity differentiate the affection from diabetes mellitus. Whether or not "primary polyuria" and polydipsia" should be considered as two distinct affections is doubtful. The writer's feeling is that they should not, as the clinical features in the two are practically identical.

Prognosis.—Idiopathic diabetes insipidus is much the more benign of the two forms. There is usually no marked emaciation, and the cases have been known to last for fifty years. The prognosis is less favorable in the secondary or symptomatic cases. Emaciation is often rapid and an early fatal termination may ensue. The length of life depends largely on the seat and nature of the causal organic lesion.

Treatment.—This is on the whole most unsatisfactory. Once the polyuria is established, it is practically impossible permanently to relieve it. The long list of drugs recommended is ample evidence of their general inefficiency. Preparations of opium have been used with some benefit. The crude opium or extract, in half-grain doses, three times daily, and gradually increasing until a total of 4 to 6 grains daily are taken, may be tried. Codeia may be administered in the same way. The relief, palliative rather than curative, is probably due to the lessening of the sense of thirst. The commonest drug administered is valerian. Either the powdered root, given in 5 grain (0.3 gm.) doses, three times daily, and increased to a total of 2 drams (8 gm.), or the valerianate of zinc in 15 grain doses (1 gm.), increased to 30 grains (2 gm.), three times daily, may be tried. Preparations of ergot have a good reputation, and to a certain extent, justifiably so. Ten minims of the tincture or fluidextract, three times daily, may be tried, and it is not infrequently followed by an appreciable reduction in the amount of urine. The benefit is temporary and symptoms of ergotism must be guarded against. According to Eric Meyer, theocin seems to increase the functional activity of the kidneys. After its administration, the specific gravity is increased, and there is no increase in the amount of urine. It may be given in 0.3 gram (5 grain) doses, three times daily.

As it is probable that a larger percentage of cases are due to cerebral lues than is generally supposed by the profession, a luetic history should be carefully inquired for, and late syphilitic manifestations searched after. Where there are marked cerebral symptoms, potassium iodide and mercurial inunctions should be given a thorough trial. In the 4 of 9 cases in which syphilis was believed to be the cause of the disease, there was marked improvement in the cerebral manifestations, in the general health, and a striking increase in the weight in all instances

after a thorough course of luetic treatment. There was, however, no material diminution in the amount of the urine.

Considering the ease with which the pituitary can now be attacked surgically, it may be hoped that the striking polyuria and polydipsia will be relieved by operation in cases with pituitary lesions.

When a patient comes under observation, it is well to reduce the fluids a pint a day, so long as there is a corresponding reduction in the amount of urine. When the reduction of urine ceases to follow the reduction in fluids, no further limitation of the latter should be made, as it means that the patient is abstracting fluids from his own tissues. For the thirst, the usual acidulated drinks may be tried. Investigators have emphasized the importance of carefully regulating the diet in each individual case. It must vary with the capacity of the kidney to concentrate urine. This is ascertained by determining the ability of the kidneys to excrete salt and urea. For this purpose the patient is put on a diet containing a constant quantity of salt and protein. Gradually the salt is lessened, and later the protein, or, after a few trial days, the patient may be put on a diet recommended by Tallquist. This consists of 1000 gm. of potato purée, 100 gm. butter, 150 gm. bread, and 500 cc. tea, and is poor in salt and protein. If the quantity of urine promptly decreases with the change in diet, it is evident that the case belongs to the renal type or is dependent upon an organic basis. If no diminution in the output of urine exists the polyuria is believed to depend on a functional neurosis. Confirmation of these results can be obtained by observing whether the polyuria increases by adding salt and protein to the diet. A patient may be kept for months on a daily intake of 5 to 6 grams of salt without injurious results. The protein should not be reduced below 50 grams daily. The essential feature in the diet is the moderate restriction of salt and protein. Among salt-free foods may be mentioned fresh vegetables, fruits, rice, sago, tapioca, cornstarch, fresh butter, eggs, fresh meat, and fish.

Herriek reported a case in which a remarkable reduction in the urine followed the withdrawal of 5 cc. of cerebrospinal fluid by lumbar puncture.

CHAPTER XVIII

GOUT

By THOMAS B. FUTCHER, M.B.

Definition.—A disorder of purin metabolism characterized by an excess of uric acid in the circulating blood, and, usually, by an arthritis, the distinguishing feature of which is the deposition of sodium biurate in the peri-articular cartilages and tissues.

Incidence.—Gout is not so rare a disease in this country as the text-books would lead us to suppose. If physicians will recognize the fact that there is, probably, no such affection as chronic rheumatism, and that the vast majority of cases of chronic arthritis are either gout, arthritis deformans, or some form of infectious arthritis, it will be found that, with due regard to the points in the differential diagnosis, a great many more cases will be justly attributed to gout than has been the case in the past. In the first twenty-four years since the opening of the Johns Hopkins Hospital, ending May 15, 1913, there have been 92 cases of gout among a total of 30,871 medical admissions, or 0.29 per cent. A comparison between the number of gout admissions to the Johns Hopkins Hospital and those admitted to St. Bartholomew's Hospital, London, for fourteen years showed that the ratio was just 2 to 3. Considering that gout is more prevalent in Southern England than anywhere else in the world, it indicates that in the vicinity of Baltimore, at least, the disease is only one-third less frequent among hospital patients than in London. It must be remembered that the better classes, in which it is more common, do not usually seek hospital treatment.

Etiology.—1. **Predisposing Causes.**—(a) *Heredity.*—Hereditary predisposition is, undoubtedly, one of the most important factors and plays a part in from 50 to 75 per cent. of the cases. This is particularly true with the well-to-do class. Scudamore states that out of 523 gouty patients, 309, or 59 per cent., gave a history of the disease in the parents or grandparents. Garrod found that the predisposition was inherited in 50 per cent. of his hospital patients. In his private cases, however, he believed that the tendency was inherited in 75 per cent. In the first 63 Johns Hopkins Hospital cases there was a history of gout or "rheumatism" in 20, or 31 per cent. It would appear, therefore, that gout in the United States is acquired or "free-hold," rather than inherited or "copy-hold," to use the classification of Sir William Browne. It is an interesting feature that, although the women of gouty families may escape gouty manifestations, they are more likely to transmit the disease to their offspring than are the men. A grandson may inherit gout from

a gouty grandfather through a mother who has never shown any manifest symptoms of the disease. Gout acquired from extrinsic causes may be transmitted to the offspring.

(b) *Age, Sex, and Race.*—Although, in inherited gout, infants at the breast have shown manifestations of the disease, it is a rare affection in infancy and childhood. This is illustrated by Scudamore's statistics of 515 cases, in which only 4 occurred before the age of seventeen, the youngest being eight years old. There were but 13 in the first two decades. When gout appears in a very young person it is nearly always inherited. In our series of 92 cases, the ages on admission to the hospital, according to decades were as follows: One to ten, none; eleven to twenty, 1; twenty-one to thirty, 5; thirty-one to forty, 17; forty-one to fifty, 28; fifty-one to sixty, 25; sixty-one to seventy, 13; seventy-one to eighty, 3. The general statement is that the initial attack makes its appearance most frequently in the fourth decade.

Males are much more liable to the disease than females. In fact it is rare in women until after the child-bearing period is over. Since the time of Hippocrates, the relative immunity in women has been attributed to the influence of the catamenia. Of 80 cases collected by a special commission of the French Academy, only 2 were in females. Of 124 cases admitted to St. Bartholomew's Hospital, in fourteen years, 24 were in women. In our series of 92 cases, there was only 4 in females. Gout in women is usually inherited. Their relative immunity is undoubtedly due, in large part, to their not being exposed to the exciting factors to the same extent that men are.

The colored race does not escape. In the Johns Hopkins Hospital series there were 6 male negroes.

(c) *Alcohol.*—It is probable that alcohol heads the list in importance among the predisposing causes. The fermented beverages, such as wines, particularly port and sherry, beer, ale, and porter, are much more injurious than the distilled liquors—whisky, brandy, rum, and gin. The quality of the alcohol seems to be, therefore, as important as the quantity. In Scotland, where whisky is the prevailing drink, gout is much less prevalent than in Southern England, where beer is the chief beverage. Investigation has failed to explain this difference in the action of the alcohol. It is apparently not due to the greater acidity of the fermented beverages, nor to the greater percentage of sugar or salines contained in them. Although the lighter beers of this country are considered less potent as an etiological factor than the heavier beers of England and Germany, the analysis of our series seems to show that beer is the chief etiological factor in the United States.

Beebe has advanced evidence showing that alcohol interferes only with the metabolism of exogenous purins, that is, those ingested with the food. It has been shown that the liver contains a uricolytic enzyme, which oxidizes uric acid into carbon dioxide and ammonia. Alcohol is known to interfere with oxidative processes in the liver and it is possible that its injurious effect in gout is due to interference with the action of this special enzyme. Unfortunately for this theory, although this uricolytic enzyme has been found in the liver and kidneys of mamma-

lians, it has not yet been conclusively shown to exist, although Schittenhelm has advanced some proof to show that it does in man.

(d) *Food and Exercise*.—Gout undoubtedly is a penalty of high living. Rich, nitrogenous foods, particularly the red meats and game, have always been held to be especially injurious. There is a growing tendency, however, to place less importance on the quality of the food and more on the quantity, and habits in regard to exercise. Overeating and the leading of a sedentary life are probably most important factors. Sydenham stated the case clearly when he wrote: "Great eaters are liable to gout, and of these the costive more especially. Eating as they used to eat, when in full exercise, their digestion is naturally impaired. Even in these cases, simple gluttony and free use of food, although common incentives, by no means so frequently pave the way for gout as reckless and inordinate drinking." Neither the quality of the food nor its quantity does so much harm as the fact that it is "unearned by muscular exertion," as Ewart puts it. We must remember that gout is not confined to the rich, however. Osler says: "In England the combination of poor food, defective hygiene, and the consumption of excessive malt liquors, makes 'the poor man's gout' a common affliction." These were the conditions that largely prevailed in our series.

(e) *Effect of Lead*.—Musgrave, Huxham, and Falconer (1772) called attention to the association between lead-poisoning and gout, but it remained for Garrod to show the importance of lead as an etiological factor. He found that 33 per cent. of the gout patients that came under his care in hospital practice, had at some period of their lives suffered from lead-poisoning, and had for the most part been plumbers or painters. An analysis of our first 63 cases showed only 3 with positive evidences of lead-poisoning. One had lead colic, and 2 had a blue line on the gums. Six others had occupations exposing them to possible lead infection. Of the 9 patients, 6 were painters, and 3 were tinnerns. Thus in 9 of the 63 cases, or 15 per cent., lead was probably a contributory etiological factor.

We do not know in just what way lead infection predisposes to gout. Garrod found that the blood of patients suffering from lead-poisoning contained an excess of uric acid. He pointed out also that these patients were liable to develop chronic nephritis, and drew the conclusion that the increased amount of uric acid in the circulating blood resulted from a renal insufficiency. The majority of subsequent investigators have supported this view. Sir Dyce Duckworth holds that the lead acts injuriously through its effects produced on the nervous centres.

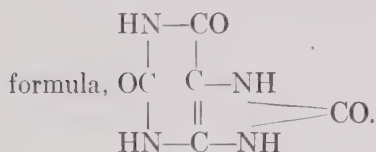
(f) *Occupation and Physique*.—As stated, those whose occupations bring them into constant contact with lead, such as painters, plumbers, and enamellers, and to a less extent, tinnerns, are liable to be attacked. Bartenders and employees in breweries, owing to the opportunity for free indulgence in the use of malt liquors, are also very prone to the disease. One rarely sees gout in a weakly, undersized, and poorly nourished individual. Persons of large frame, good physique, and with a tendency to obesity, are the ones who usually manifest the disease.

(g) *Traumatism* is thought by many to be a contributory factor. The prevalence of the attacks in the big toe joints has been in part explained by the liability of this articulation to injury while walking or from pressure by an ill-fitting shoe.

2. **Metabolic Causes.**—From the chemical standpoint, the etiology of gout is closely connected with nitrogen metabolism, and with the formation and excretion of certain compounds of which nitrogen is a component. Since 1797, the year in which Wollaston demonstrated that the gouty deposits about the joints contained uric acid, the vast majority of those who have studied the disease have concluded that it is connected in some way with the formation and elimination of uric acid. There is a steadily growing conviction among the best students of this disease at the present day that uric acid plays little or no part in the actual etiology of gout. Although an excess of uric acid in the blood and of its salts in the tissues dominates the picture in well-marked cases, this excess of uric acid is held to play a secondary part and to be a mere weapon of the disease. There is no experimental proof showing that an excess of uric acid causes any special toxic symptoms. The growing belief is that gout is really a disease of intermediary purin metabolism. This receives support from the very important recent discovery that certain tissue ferments play a most important rôle in the metabolism of the purin bodies. While it will seem hard for us to divorce our minds from the long-prevailing uric acid theory of gout, the following considerations of purin metabolism indicate strongly that we shall probably have to do so.

(a) *Uric Acid Metabolism under Normal Conditions.*—To better appreciate the metabolic disturbances in gout, it is important to understand, as fully as our present knowledge permits, the chemistry of uric acid and its closely allied compounds under physiological conditions.

Uric acid has the empirical formula $C_5H_4N_4O_3$ and the rational

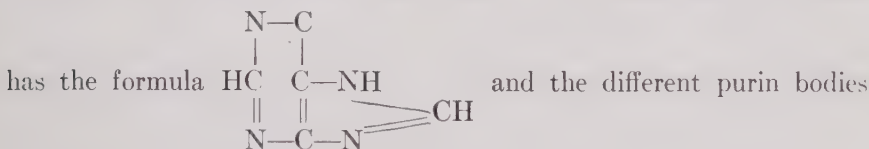


The generally accepted view, at the

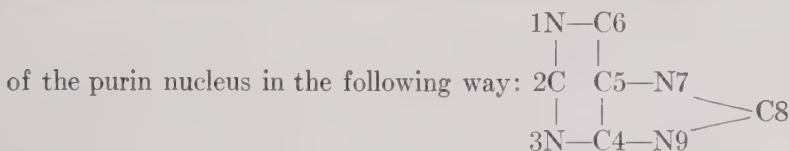
present time, is that it is derived partly from nuclein resulting from the disintegration of cell nuclei, and partly from the hypoxanthin, which is produced as a product of muscle metabolism. At least 4 other nitrogenous compounds are known to be derived from nuclein. These are xanthin ($C_5H_4N_4O_2$), hypoxanthin ($C_5H_4N_4O$), guanin ($C_5H_5N_5O$), and adenin ($C_5H_5N_5$). In addition to these, there are 5 other compounds closely allied to them in general structure. They are as follows: Heteroxanthin ($C_6H_6N_4O_2$), paraxanthin ($C_7H_8N_4O_2$), episarkin ($C_4H_6N_3O$), carnin ($C_7H_8N_4O_3$), and epiguanin ($C_6H_7N_5O$).

These 10 nitrogenous compounds were given the name alloxuric bodies (*alloxur körper*) by Kossel and Krüger, whereas the last 9 constitute the alloxuric, xanthin, or nuclein bases. The term "alloxuric"

was applied to them because each was made up of a combination of an alloxan and urea nucleus. Emil Fischer has shown that there is a very intimate relationship between the various members of this group, and has demonstrated the remarkable fact that a number of them can be prepared synthetically. He found that they are all derived from a compound $C_5H_4N_4$, which he termed "purin," having a carbon-nitrogen nucleus, the "purin nucleus," as a basis. Purin, according to Fischer,

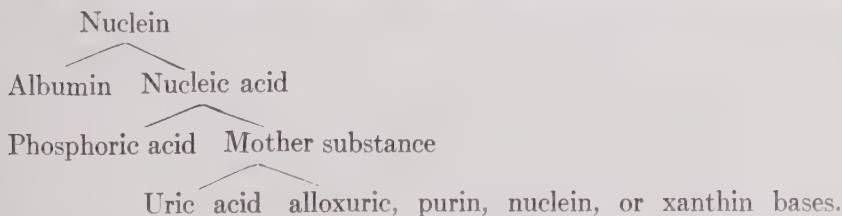


are derived therefrom by the substitution of the various hydrogen atoms by hydroxyl, amide, or alkyl groups. In order to designate the different positions of substitution, Fischer has proposed to number the 9 atoms



In studying the structural formula of uric acid given above, it will therefore be seen that it is 2.6.8 trioxypurin. Xanthin, accordingly, is 2.6 dioxypurin; hypoxanthin is 6. oxypurin; adenin is 6. amino purin; and guanin is 2. amino-6. oxypurin, etc. To summarize, therefore, the alloxuric or purin bodies include uric acid, together with the alloxuric, purin, nuclein, or xanthin bases. The purin substances are supposed to be contained in the nucleic acid of the cell nuclei in the form of a loosely combined phosphorus-containing body—the nucleotin-phosphoric acid, as Schmiedeberg has termed it. Intimately related to the above purin bases are the vegetable bases, caffeine, theobromine, and theophyllin, all of which are methyl xanthins.

The close relationship between uric acid and the xanthin or purin bases and their common origin from nuclein are shown by the following scheme:



The purin bodies from which uric acid is mainly if not entirely derived, come from two sources. Burian and Schür have designated them the "exogenous" and "endogenous" purins. The exogenous purins are those introduced with the ingested food, whereas the endogenous purins are those derived from the nucleins of the body and, according to recent

investigations, chiefly from muscle metabolism. In the same manner, we speak of "exogenous" and "endogenous" uric acid, when it is derived from these respective sources. By the use of a purin-free diet (such as milk, eggs, butter, cheese, white bread, rice, sago, and fruits) it has been possible to estimate the quantity of nuclein derivatives or purin bodies which arise solely as a result of cellular processes. In 1905 Burian demonstrated that the muscle purins, particularly hypoxanthin, are the chief source of the endogenous uric acid. He found that muscular exertion is always accompanied by a decided rise in the output of uric acid. The investigations of Burian and Schur show that the endogenous purins excreted in the urine in twenty-four hours vary from 0.1 to 0.2 gram, expressed in terms of nitrogen, of which one-fiftieth to one-tenth is in the form of xanthin or purin bases and the rest as uric acid. On such a diet, Rockwood, working in Chittenden's laboratory, found that the daily output of uric acid in a normal individual ranges between 0.3 and 0.4 gram. He also confirmed the observations of Burian and Schur, that a given individual shows a certain degree of constancy in the daily excretion of uric acid. In other words, the elimination of endogenous uric acid is constant for each individual; that is, it is an individual factor dependent, probably in part, upon the weight of the individual or of the contained organs and tissues. The figures of Burian and Schur given above do not represent the entire amount of nuclein decomposed in the body. The remainder is transformed by specific enzymes of the liver and other organs (to be referred to later) and excreted as urea, or as bodies intermediate between the purin bodies on the one hand and uric acid and urea on the other. Allantoin is one of these intermediate bodies. Wiener holds that glycocoll is the only decomposition product of uric acid. Of the total purin bodies of the urine, nine-tenths is excreted as uric acid and one-tenth as the xanthin or purin bases.

Seat of Formation of Uric Acid.—Until a very recent date, we possessed no definite knowledge as to the seat of formation of uric acid, nor in what organs the various purin bases were contained or oxidized into higher oxidation products. Garrod, Latham, and Luff hold that the uric acid is formed in the kidneys. Zaleski, after extirpating the kidneys of snakes, and von Schröder, after removal of these organs in birds, have shown that there is an accumulation of uric acid in the blood and tissues of these animals. This goes to show that the kidneys of birds and snakes, at least, are not the only organs that produce uric acid. Hammarsten claims that we have no direct proof that uric acid is formed in the kidneys and the general opinion is against the view that uric acid is formed in these organs.

It is probable that uric acid originates in the system only as a result of oxidative processes. Experimentally, the synthetic formation of uric acid has been demonstrated. By passing ammonium lactate through the livers of geese, Kowaleski and Salaskin, in 1901, showed that it was synthetized into uric acid, as indicated by the great increase of the latter in the blood leaving the liver. There is no conclusive evidence, however, that a similar synthetic formation of uric acid occurs in the human subject, although it is possible that it may occur.

Physiologists and physiological chemists have demonstrated that many of the chemical transformations in the body, previously not understood, are really due to the action of specific ferments or enzymes. We are indebted to Walter Jones and his associates, to Schittenhelm, Brugsch, and Burian for our knowledge concerning these ferments and the part they play in the intermediate metabolism of the purins. To summarize, these enzymes according to Brugsch and Schittenhelm may be divided into four groups: (1) the *nucleases*, which have the power of liberating the purin bases from their combination as a component part of the tissue nucleoproteids; adenin and guanin are thus set free; (2) the *desamidases*, which by splitting off the amino groups and by oxidation, produce, from adenin and guanin, hypoxanthin and xanthin respectively. The enzyme which transforms adenin into hypoxanthin is called *adenase*, whereas that which converts guanin into xanthin is termed *guanase*; (3) the *oxidases*, which oxidize hypoxanthin and xanthin into uric acid; and (4) the *uricolytic enzyme uricase*, which oxidizes uric acid into carbonic acid and ammonia through one of the intermediate stages.

The work of Levene and Jacobs on the structure of nucleic acid showed that when phosphoric acid is removed by the action of gland extracts two nucleosides are formed. Guanosine, one of these, is composed of d-ribose and guanin, and by acid hydrolysis gives guanin. Adenosine, the other, is composed of d-ribose and adenin, and this similarly yields adenin. They have been able to transform these two nucleosides, which are amido-derivatives, into two other nucleosides, xanthinosine and inosine respectively, which are the corresponding compounds. Walter Jones and Amberg, by the use of glandular extracts, have shown that a similar transformation is brought about by the existence of two other desamidases, *guanosine-desamidase* and *adenosine-desamidase* respectively. The xanthosine and inosine are further converted into xanthin hypoxanthin by a process of hydrolysis, and these in turn by the action of the *oxidases* are converted into uric acid.

Levene has shown that the nucleases and desamidases are found in nearly all the organs studied; as well as in some of the digestive juices. The oxidases are found in many of the organs. The uricolytic enzymes have been demonstrated in the mammalian kidney and liver, and it is not yet definitely demonstrated that they are present in man. Schittenhelm has shown, however, that when human beings are fed nucleic acid there is not only an increase in the output of uric acid, but also of urea, from which he assumes that the uricolytic enzyme is also present in human tissues.

For the above enzymes to perform their functions properly, there must be a proper relationship between the quantity of the purin bodies to be acted on and the various ferments. Mendel has shown that if the purin bodies be in excess, their thorough oxidation does not take place, and instead of their being largely oxidized to urea, an intermediate oxidation product—allantoin—is produced, and excreted in the urine in excess.

The exogenous purins taken in food are either in the form of the free bases adenin, guanin, hypoxanthin, xanthin, or as combined purins and

nucleoproteins. Of the free purin bases in the ordinary foodstuffs, it is the oxypurins, hypoxanthin, and xanthin that the body has mainly to deal with, as they are contained in large amounts in meat broths and extracts. They are, however, easily oxidized into uric acid, and excreted as such, or further oxidized into urea or other products by the special oxidase. When combined purins are introduced in the form of nucleins and nucleoproteins, adenin and guanin are liberated by the action of nuclease. The continuance, unchanged, of these two bodies, depends upon the presence and action of the two enzymes, adenase and guanase. If these are present and active in normal degree, we can conceive of a rapid conversion into hypoxanthin and xanthin and then by the action of oxidase into uric acid. If the enzymes be deficient, then the adenin and guanin will circulate unaltered in the blood, for a time at least. Chittenden offers the suggestion that the prolonged circulation of these aminopurins may account for the renal changes in certain diseased conditions, presumably gout, for it has been shown that when adenin is administered to dogs and rabbits, it causes anatomical changes in the tubules of the kidneys, with deposits of spheroliths of uric acid and ammonium urate in the kidney substance.

Since the division of uric acid into the exogenous and endogenous forms, it has been held, until a very recent date, that the endogenous uric acid resulted entirely, or almost entirely, from the nuclein derivatives derived from the destruction of the nuclein of the glandular and tissue cells. In 1905 Burian showed that this view is erroneous. He finds that only a very small amount of the endogenous uric acid has its origin in the nucleoproteins of disintegrating tissue cells or leukocytes, the larger part being derived from the purin-base hypoxanthin, which is continually being formed as a metabolic product of living muscle tissue. It is not possible to go fully into this important observation here. It is sufficient to say that Burian's work opens up a new chapter in purin metabolism, bearing on the production of endogenous uric acid. In the resting state, muscle is continually giving up to the blood a certain amount of uric acid formed at the expense of the hypoxanthin which originates within its own tissue. The oxidation of the hypoxanthin to uric acid is accomplished by the specific oxidase which the muscle itself contains. Burian points out that this oxidase must be so located that the hypoxanthin is converted into uric acid just as it is passing from the muscle fibre into the blood or lymph, since muscle itself never contains any uric acid, only purin bases. He also believes that a certain amount of the uric acid is at once decomposed by the other oxidizing ferment which destroys this acid.

The portion of the endogenous uric acid that results from the disintegration of the nuclei of body cells and leukocytes is also fully believed to be the result of the action of the specific ferments already described. It will thus be seen that these investigations have given an entirely new conception of the seat and method of formation of uric acid.

Form in Which Uric Acid Circulates in the Blood.—The blood normally contains traces of uric acid. In health and on a purin-free diet it does not exceed 1 to 3 mg. per 100 cc. of blood. It is not possible here to

review the various ideas that have been advanced as to the form in which the uric acid circulates in the blood in health. The present accepted views is that of Gudzent, who holds that it exists as the biurate of soda, or as it is now called, the monosodium urate. Gudzent has shown that this salt occurs in two isomeric forms. At first it is in the *laktam* form, which is unstable but soluble in blood serum to the extent of 18.4 mg. per 100 cc. of blood. In the course of time it passes into the *laktim* form, which is only soluble to the extent of 8 mg. per 100 cc. of blood. This difference in solubility is probably of importance in helping to explain the deposition of uric acid in the tissues.

Daily Excretion of Uric Acid.—The amount of uric acid eliminated daily in the urine by the healthy adult of average weight, when on a mixed diet, ranges between 0.4 and 1 gram. Hammarsten gives 0.7 gram as the average. According to Brugsch 50 per cent., and according to Umber 90 per cent. of the endogenous purins are excreted in the urine as uric acid, with traces of hypoxanthin and xanthin.

(b) *Uric Acid Metabolism in Gout.*—There is undoubtedly marked disturbance of nitrogenous metabolism in gout. The total nitrogen equilibrium is disturbed; a nitrogen retention occurs. Since the adoption of the classification of purins into the "endogenous" and "exogenous" varieties, too little time has elapsed and too few investigations have been published, to draw absolute conclusions as to how the metabolism of each is affected. The studies of Reach, Kaufmann, Vogt, and Chalmers Watson show that in gout the exogenous purins are more slowly excreted than in health, and that in some cases there is a distinct retention. Vogt gave rich purin-holding food to a gouty patient and to a healthy individual, and found that in the former there was a delayed excretion, and definite retention of the purin bodies. It can safely be concluded that exogenous purins, in part at least, lead to an excess of the nuclein derivatives in the blood-stream. There is no question but that the metabolism of the endogenous purins is also markedly disturbed in gout. This will probably be best shown by a consideration of the amount of uric acid excreted in the urine as well as of that present in the circulating blood.

The Excretion of Uric Acid in Gout.—Garrod was the first to claim that there is a diminished excretion of uric acid in gout. He believed that this was true both of the acute attack as well as of chronic gout. Since the adoption of more reliable methods of quantitative analysis in recent years, Garrod's results have not been confirmed *in toto*. Minowski states that the following conclusions may be drawn: (1) The daily excretion of uric acid, in the intervals between acute attacks, ranges within the same limits as does the excretion in healthy individuals. (2) In chronic gout, even in those cases in which there is marked deposition of biurates in the tissues, a constant diminution in excretion of the uric acid has not been definitely proved. (3) Immediately preceding and following an attack there is regularly a diminution in the amount of uric acid eliminated in the urine, whereas during the attack the uric acid output is often markedly increased. The writer, however, has found in some cases of chronic tophaceous gout a marked diminution in the uric acid elimination between acute attacks.

To what are these variations in the uric acid excretion due? Various possibilities present themselves. The diminution in the excretion of uric acid before the onset of an acute attack may be interpreted as meaning either a diminished uric acid production, or a temporary diminished capacity on the part of the kidneys to excrete uric acid. The sudden deposition of uric acid salts about the joints and in the tissues affords a third possible explanation. The increased uric acid output during an attack may be due to an increased uric acid production, or to the possibility that the previously retained uric acid is temporarily excreted in increased quantity. The variations in the excretion may further be explained on the supposition that at times a smaller, and at other times, a larger, part of the uric acid in the organism is metabolized into other waste products, such as urea.

The Uric Acid in the Blood in Gout.—Practically all observers agree that there is a marked increase of the uric acid in the circulating blood. Garrod first demonstrated this excess by quantitative analysis and, also, by his well-known "thread-test." Klemperer, who was unable to demonstrate uric acid in normal blood, found in three cases of gout 0.067, 0.088, and 0.0915 gram of uric acid in 1000 cc. of blood during an acute attack. Magnus-Levy made 34 analyses in 17 cases of gout, and found the uric acid to range between 0.021 and 0.1 gram in 1000 cc. of blood. The same observer also sought to ascertain whether there was any regular difference in the amount of uric acid in the blood during an acute attack and in the intervals. Of 10 cases studied, the uric acid was the same during the acute attack as in the intervals in 5; greater in 2; and less in 3. It cannot be said then that there is by any means a constant increase in the amount of uric acid in the blood during an acute attack over that present in the intervals.

The Alkalinity of the Blood in Gout.—The earlier methods of determining the alkalinity of the blood were very untrustworthy. Fokker and others deny that the blood of the normal individual is alkaline, claiming that it is neutral. However this may be, it may be briefly stated that, with modern methods of determining the alkalinity of the blood, there is no definite support of the view first advanced by Garrod that the blood is less alkaline in gout than in health and less capable of holding the uric acid salts in solution.

Causes of the Excess of Uric Acid in the Blood.—The evidence on this point has been analyzed by Wiener in his excellent review of uric acid in its relationship to gout. He claims that there is no special evidence to point toward the excess being due to deficient oxidation. Klemperer has shown that the blood of the gouty individual still possesses the power *in vitro* of destroying uric acid, presumably by oxidation. Wiener's analysis was published previous to the appearance of the recent studies showing the important part that specific ferments play in the formation and destruction of uric acid. As already pointed out, the excess of uric acid in the blood in gout may eventually be shown to be due to a deficiency in the uricase which normally converts it into urea and other products.

Although the increase in the uric acid in the blood and urine in leukemia and pneumonia is undoubtedly due to increased formation, resulting

from increased nuclein destruction, the evidence is not nearly so convincing in the case of gout. We know that uric acid is formed partly by oxidative processes from the nucleins and partly by synthetic formation in the liver. There is no definite evidence of any increased nuclein destruction in gout. There is no leukocytosis, excepting a slight temporary one during the acute febrile attacks; so an increase in the leukocytes with their increased disintegration cannot explain the increase of uric acid in the blood. We have no definite evidence to point toward an increased synthetic formation of uric acid in the liver.

There are some points favoring the view that the excess of uric acid in the blood is due to diminished excretion by the kidneys. In support of it is the prevalence of, and, according to Levison, the constant association of an interstitial nephritis in gout. Most authorities are inclined to consider the nephritis as a result of the gout. The influence of nephritis on uric acid excretion and its deposition about the joints is shown by Ord and Greenfield's statistics. Out of 96 cases of renal disease there were biurate deposits in the joints in 18. Levison claimed that it was always with contracted kidneys that this deposition occurred. This was supported by the investigations of Luff, who found biurate deposits in the joints in 20 out of 26 cases of chronic interstitial nephritis. These observations tend to show that in interstitial nephritis there is some condition produced, presumably a retention of uric acid, which favors the latter's deposition in the joints. In support of the retention theory may be mentioned the researches of Hans Vogt and Reach, who found that the excretion of uric acid after the ingestion of nuclein or nuclein-containing food is much less marked in the gouty than in the healthy individual. Schreiber claims, contrary to Levison's view, that interstitial nephritis is not always present in gout. In these cases without organic renal disease, Minkowski is inclined to support the older view of Garrod that it is possible that a functional disturbance of the kidney may occur which lessens its ability to excrete uric acid. He favors the retention theory as the cause of the excess of uric acid in the blood. He and His have advanced the view that the uric acid in gouty individuals circulates in the blood in a different organic combination from that in which it exists in the blood of healthy persons, and that consequently the kidneys are functionally incapable of eliminating it as in health. A very strong argument against this retention theory is the fact that, even in cases with well-marked nephritis, it is well known that the kidneys are capable of excreting uric acid in quantities considerably above the upper limit for normal for two or three days after the onset of an acute attack.

The opinion of the majority of investigators of this disease seems to favor at the present time the view that the excess of uric acid in the blood is due to retention. If it is demonstrated more conclusively at a later date that there is a uricolytic ferment, *uricase*, in human organs whose function it is to convert uric acid into its end-products, we may have to alter this view.

Theories of Gout.—Garrod held that in acute gout the alkalinity of the blood is lessened and the uric acid of the blood is increased owing to deficient power of elimination on the part of the kidney. The latter

is due, usually, to organic disease but may result from a purely functional disturbance. He attributes the deposition of sodium biurate in the tissue to the diminished alkalinity of the plasma, which is unable to hold the uric acid combination in solution. During an acute paroxysm there is an accumulation of the urates in the blood and the local inflammation is caused by their sudden deposition in crystalline form about the joints. This theory has had many supporters and in large part can be accepted, but any explanation based on the degree of alkalinity of the blood must be received with some scepticism.

Since it has been shown that uric acid does not circulate in the blood as sodium quadriurate as Sir William Roberts claimed, his theory based on this view is no longer tenable.

Ebstein held that the local manifestations of gout are due to nutritive tissue disturbances which lead to necrosis. He found, after a study of many of the affected tissues in gout, that one change is common to them all, independently of the urate crystallization, and that is, a necrosis of the parts in which such deposition takes place. He believes that this necrosis is primary, and that it is as characteristic as the biurate deposit. Both changes must coexist in any tissue in order to constitute a true gouty lesion, and he has found such lesions in the kidneys, in hyaline and fibrocartilage, and in tendons and connective tissue. He called attention to the early stages of the necrotic process, in which he found no deposition of the biurates, and consequently maintained that a nutritive tissue disturbance is the primary factor, and uratic deposition a secondary one in the gouty process, the latter not occurring until death of the tissue takes place. Von Noorden supports Ebstein's views, and believes that the tissue necrosis is due to the action of a special ferment.

In 1784 Cullen advanced the theory that gout was primarily due to an affection of the nervous system. According to this view there is a basic arthritic stock—a diathetic habit of which gout and rheumatism are two distinct branches. The chief advocate of the nervous theory at the present day is Sir Dyce Duckworth, who at first held that disease of a special tract in the cord was the cause of the tissue lesions in gout. Although he no longer insists that gout is due to a lesion of any particular column of the cord, he just as strongly insists that it is essentially of nervous origin. The influence of depressing conditions, mental and physical, in precipitating an attack of gout, points strongly to the part played by the nervous system in the etiology of the disease. The nervous theory has not received very general support.

In recent years attention has been attracted to the xanthin or purin bases as a possible cause of gout. Kolisch found that although the uric acid excretion is diminished, yet the total output of the alloxuric or purin bodies was increased. He believed that the xanthin bases normally are finally oxidized into uric acid in the kidneys, but that in gout the kidneys are diseased, and their power to oxidize the xanthin bases is consequently impaired. His results were obtained by methods shown later to be inaccurate, and Sülzer, Laquer, and Magnus-Levy failed to confirm them. Whatever part the xanthin bases may subsequently be shown to play in the etiology of gout, up to the present they have not

been shown to exert an important influence. Undoubtedly some of the xanthin bases are definitely toxic. Kolisch and Croftan have produced arterial and renal lesions by injecting hypoxanthin into animals. I. Walker Hall confirmed these results and also produced parenchymatous changes in the liver by long-continued injections of hypoxanthin.

Brugsch and Schittenhelm hold that gout is due to the absence or destruction of the uricolytic enzyme *uricase*, which they claim is present normally in the liver and the function of which is to convert uric acid to allantoin. This still lacks confirmation.

It has been claimed by some that glycocoll is found quite frequently in the urine of gout patients, and it has been thought that it may be a factor in the causation of the disease. As yet, too little is known to express any definite opinion on this point. Its relationship to uric acid is well known. On heating the latter with concentrated mineral acids in sealed tubes to 170° C., it splits up into glycocoll, carbon dioxide, and ammonia.

Summary of Our Knowledge Concerning the Chemistry of Gout.—It will be seen from the foregoing that there is much divergence of opinion regarding the true cause of gout. The subject still awaits a definite elucidation. Whatever may eventually be determined to be the actual cause, there is a growing impression that uric acid plays only a secondary part, and I. Walker Hall, who has been one of the most active students of the disease, recently asserted that it is in no way an etiological factor. On one point all investigators agree, and that is that there is marked increase in the uric acid circulating in the blood. Whereas it may be demonstrated later that this excess of uric acid in the blood is due to deficient oxidation of uric acid in the liver or to the absence of a supposed uricolytic ferment, the balance of opinion at the present time seems to favor the retention theory. The deposition of biurates in the tissues and about the joints appears to be due to some factor other than the mere presence of an excess of uric acid in the blood. Whether or not a primary tissue necrosis is a necessary antecedent to the biurate deposition still lacks definite proof. There is no positive evidence that there is a greater excess of uric acid in the blood during an acute exacerbation of the disease than in the intervals. It seems impossible to attribute the deposition of biurates to diminished power of the blood to hold the uric acid in solution, owing to the diminished alkalinity of the serum, as claimed by Garrod, Haig, and others.

The brilliant investigations of the last fifteen years have taught us much concerning the intermediary metabolism of the purin bodies. Various enzymes have been found whose function it is to transform the various purin bodies into each other. The nucleases split off the purin bases adenin and guanin from the nucleoproteins. The desamidases, adenase and guanase, convert adenin into hypoxanthin and guanase into xanthin respectively. The ozidases oxidize xanthin and hypoxanthin into uric acid. For the lower animals it has been shown that there is a uricolytic ferment, *uricase*, which oxidizes uric acid into carbonic acid and ammonia. Schittenhelm has brought forward some evidence to show that such an enzyme is also present in the human individual. If

this observation be confirmed, it is possible to conceive how certain factors, one of which is believed to be alcohol, could inhibit the action of this ferment, this leading to diminished destruction of uric acid and its consequent increase in the circulating blood.

While the arthritic manifestations of gout are usually explained as being due to the mechanical irritation of the biurates locally deposited, the uric acid theory does not so satisfactorily explain the nervous and visceral manifestations of the disease. There are many who oppose this view as to the cause of the joint pains in acute attacks. No other satisfactory explanation has been advanced. It seems more probable to the writer that the pain is actually due to the acute inflammation which occurs, with stretching of the peri-articular tissues and consequent irritation of the surrounding nerves. We have no positive indication that uric acid itself is definitely toxic in the sense in which we use the term to designate a chemical poison. Animals have been made to ingest large quantities of uric acid with their food, and urates in solution have been freely injected into their veins, without causing any signs of poisoning. It may be that some other toxic agent is responsible for the symptoms of irregular gout. Roberts thinks, however, that even in this form, the symptoms may be due to the actual deposition of sodium biurate in the fibrous tissues in and about the nervous system and in the gastro-intestinal tract. He suggests that the failure to microscopically demonstrate such deposition may be due to insufficient search or to the possibility of the biurates subsequently disappearing.

Pathology.—The Blood.—There is always an excess of uric acid, as was first demonstrated quantitatively by Garrod in 1848. Normally the blood does not contain more than 1 to 3 mg. in 100 cc. of blood. Klemperer found as high as 9 mg. and, in 17 cases, Magnus-Levy found the amount to range between 2 and 10 mg. in 100 cc. of blood from gout patients. Roethlisberger has devised a simple method of determining quantitatively the uric acid in the blood. Probably the most accurate method is that recently devised by Folin and Denis.

There is no special tendency to the development of anemia. The leukocytes are not increased except slightly during an acute attack. One of our hospital cases with tophaceous gout eventually died of pernicious anemia. Neusser occasionally found that there is an eosinophilia, and Chalmers Watson has seen numerous degenerated myelocytes during acute attacks. Neusser's so-called "perinuclear basophilic granules," which he considered pathognomonic of a uric acid diathesis, have been shown by the writer and others to be due to artefacts and to occur in the blood of normal individuals with the same technique. There was no association between the excretion of the alloxuric bodies and the relative abundance of these granules, as he supposed. Recent investigations tend to show that there is no constant reduction in the alkalinity as has been held by Garrod, Haig, and others. In the cases of saturnine gout, the red cells are likely to manifest the basophilic granular degeneration seen in lead poisoning.

The Joint Changes.—The characteristic lesions of gout manifest themselves particularly in and about the articulations. They are dependent

upon the deposition of uric acid in the form of sodium biurate, and on the inflammatory and degenerative processes which result therefrom.

On examining a gout joint at autopsy, the articular surfaces will be found studded with specks, streaks, or patches of white, mortar-like material. This is composed of sodium biurate deposited as long acicular crystals. It is likely to be most abundant toward the central portion of the articular surfaces. The sodium biurate is not on the surface of the cartilages but is covered over by a thin layer of cartilaginous tissue. It seldom reaches the bone and, as Garrod pointed out, rarely penetrates beyond two-thirds of the depth of the cartilage. In very advanced, chronic cases there may be actual erosion of the cartilage, but this is rare as compared with arthritis deformans. In the chronic cases, the biurate deposit often invades the capsular tissues, and may even infiltrate the skin, and lead to suppuration of a joint tophus. The biurate deposit in the cartilage can be demonstrated microscopically by examining sections cut at right angles to the articular surface; also by the simpler method of scraping off some of the articular cartilage and teasing in salt solution and examining microscopically. It is believed that the biurate is deposited from the synovial fluid of the joint cavity. In the chronic cases there is much thickening of the capsular tissues. In these there may be increased dryness of the joint; but if the patient dies during an acute attack, there is usually, particularly in the knee-joints, an excess of synovial fluid, and the synovial membrane may be reddened and injected. The synovial fluid is usually somewhat turbid, and contains a varying number of polymorphonuclear leukocytes and occasionally acicular crystals of sodium biurate.

There is considerable diversity of opinion, regarding the essential cause of the biurate deposition. Ebstein insisted that there is always a primary tissue-necrosis. It seems more likely that, if this view be correct, the areas of necrosis result from the toxic action of some as yet unknown poison, or to one of the intermediate purin bodies. These necrotic areas are most liable to occur in the joint cartilages and other cartilaginous and articular structures in which the normal nutritional currents are slow. In support of his view, he stated that he often found areas in which there was necrosis without biurate deposition. In these areas of coagulation necrosis, the reaction is always acid, so that the conditions are favorable for the precipitation of the uric acid in the form of the crystalline biurate. Von Noorden thinks this necrosis may be due to a special ferment. His and Mordhorst claim that the deposition of the sodium biurate is primary, and that the tissue necrosis is a secondary process. According to Roberts, the biurates are deposited most abundantly in cartilaginous tissue, because here the temperature is lowest, the circulation poorest, and, in the case of the articular cartilage, it is bathed with the synovial fluid, which is rich in sodium chloride, and which he claims favors the deposition of sodium biurate. According to Wynne, the marginal outgrowths about the gouty joints are true exostoses. The bursæ may be acutely inflamed and may contain deposits of biurate of soda.

The frequency with which biurate deposits are found in the joints

at autopsy corresponds closely with the relative frequency with which the gouty arthritis is seen clinically. Norman Moore has brought this out well in an analysis of 80 autopsies on gout patients. The joints most commonly involved are the metatarsophalangeal joints of the big toes, and frequently these are the only ones affected. Then follow the tarsal joints, ankles, knees, hands, and wrists. The elbows, shoulders, and hips are more rarely involved. Among the rarest sites are the articulations of the jaws, larynx, and sternoclavicular joints.

Situations in which Tophi Occur.—Biurate deposits occur in other situations than in the joints and their neighborhood. These are termed "tophi," a name derived from the Hebrew, and signifying "concretions." They are also known as "chalk-stones." The commonest situation for them to occur in is on the helix or anti-helix of the ear. They are also frequently found in the tendons and aponeuroses. In one case the writer saw a tophus measuring 3 by 6 cm., in the tendo Achillis. They are not infrequently seen in the subcutaneous tissue. The commonest seats of skin tophi are the extensor surfaces of the forearms, near the elbow-joint, and the neighborhood of the patella. They may be mistaken for rheumatic subcutaneous nodules. The writer has observed a patient with numerous tophi in the prepuce; another had a large group of them over the sacrum. They may also occur in the palms and soles, nose, and tarsal cartilages of the eyes. Less common situations for biurate deposits are the laryngeal cartilages, vocal cords, cranial and spinal dura mater, the pia mater, sclerotic coat of the eye, the fibrous sheaths of the nerve trunks, and the aortic valves. Enormous tophi, which may break down and suppurate, not infrequently occur about the finger- and knuckle-joints. Ebstein and Sprague have carefully analyzed the tophi, and find that they contain, on an average, 57 per cent. of sodium biurate and from 12 or 13 per cent. of calcium biurate. Somewhat similar to these tophi in man are the deposits characterizing "guanin gout" in hogs. When these animals are fed in a certain way, one sees in the muscles, ligaments, and articular tissues, small whitish deposits which are made up of guanin.

The Kidneys.—Of the visceral lesions, those of the kidneys are the most frequent and important. Nephritis is extremely common, and, according to Levison, is always present. Ebstein described two types of gout cases: (1) the "primary renal gout," and (2) the "primary articular gout." In the former, the renal disease has existed for some time, and, subsequently, articular manifestations of gout appear. Such a case occurred in a colored man, aged twenty-four years, admitted to the Johns Hopkins Hospital. For several months he had complained of the usual symptoms of chronic nephritis. There had been no previous arthritic history. A few days before his death, he developed pain and swelling of his right big toe-joint. This joint at autopsy showed the characteristic deposits of sodium biurate in the articular cartilage. The kidneys were much contracted. In the latter type, the articular manifestations antedate the onset of the clinical symptoms of nephritis. The form of nephritis usually met with in gout is that characterized by granular degeneration and marked atrophy. It is often spoken of as

the "gouty kidney." On the other hand, the arteriosclerotic kidney may be met with. Here the kidney is larger, beefy, red, and very hard. There appears to be no special difference between the kidney of saturnine and that of ordinary gout. The gouty kidney, on section, not infrequently shows white deposits of sodium biurate. In the cortical substances the deposit is scanty and occurs in specks scattered irregularly through the tissue. It is, however, most frequently seen, and most abundant, in the pyramids, occurring in streaks running in the direction of the tubules, particularly toward the apices of the pyramids. In both situations, the deposit is usually situated in the intertubular tissue, but it may also occur in the lumen of the tubules. When examined microscopically it is seen to exist as acicular crystals, just as in the gouty joints. These deposits were first described by Castelnau. They are not so frequently found as we would be at first led to infer. Norman Moore found them in only 12 out of 80 cases. Osler holds that these deposits must not, however, be always interpreted as meaning that the individual has gout, as they occasionally occur without the person having had any gouty manifestations.

Cardiovascular Lesions.—Arteriosclerosis is very common. Nearly all cases of chronic gout show marked thickening of the peripheral arteries. Whether the arterial thickening is due to the toxic action of the excess of uric acid in the blood, to that of the products of intermediary metabolism, or to the contributory factors, producing the gout—viz., alcohol, lead, or excessive food—is difficult to determine.

The combination of nephritis and arteriosclerosis with consequent increased arterial tension, frequently leads to hypertrophy of the left ventricle. The arch of the aorta is frequently involved in the arteriosclerotic process. The orifices of the coronaries may be narrowed, and the coronary vessels themselves sclerosed. The coronary involvement renders the subject liable to attacks of angina pectoris. For the same reason, myocardial changes are common, and death may result from failure of compensation. Fatty degeneration of the heart muscle occurs. A gouty pericarditis is not uncommon. In rare instances, sodium biurate deposits have been found in the aortic valves.

Respiratory System.—Sodium biurate deposits may occur in the vocal cords, and in the epiglottis and laryngeal cartilages. In rare instances the biurate crystals have been found in the sputum. Emphysema is very common in chronic gout, and the lungs may show a chronic bronchitis.

Symptoms.—**Acute Gout.**—In the initial attack there may be no premonitory symptoms. A previously healthy man of middle age retires feeling perfectly well. During the night he is awakened with intense pain, usually in the right metatarsophalangeal joint. By morning the joint is reddened, slightly swollen, and sensitive to the touch. The temperature is moderately elevated, reaching usually to between 101° and 103° F. As morning approaches, the pain, which has been agonizing and makes the patient feel as though the joint is being squeezed in a vise, gradually subsides, and, beyond having a feeling of general malaise and of anorexia, he experiences a fairly comfortable day. The next night

the attack recurs, and the pain, as Sydenham says, "insinuates itself with the most exquisite cruelty among the numerous small bones of the tarsus and metatarsus, in the ligaments of which it is lurking." There is a repetition of these attacks each night for a week or ten days, constituting a so-called "fit of the gout." For the first few days the swelling of the joint increases, coincident with which there is a gradual abatement of the intensity of the pain. The skin over the joint is reddened and shiny. The surrounding veins are slightly dilated, and, toward the end of the attack, there may be slight pitting on pressure over the joint. The inflammation never goes on to suppuration. With the subsidence of the acute swelling, the skin may desquamate. During the acute febrile period, there is a leukocytosis which may reach 20,000 per cmm. In the initial seizure both big toe-joints may be involved. On the other hand, these articulations may escape, and the tarsal and tarsometatarsal joints may be first affected. In these instances the "fit" generally lasts considerably longer. After the attack, the general health may be decidedly improved. There may be no recurrence of the acute attack for years. More commonly, however, only months elapse, and there is a tendency to periodical recurrences in the spring and fall. Premonitory symptoms occasionally precede the acute attacks for a number of days, and the victim can often predict its onset. These symptoms are quite diverse. The most prominent ones are digestive disturbances—loss of appetite, flatulence, and acidity. Nocturnal restlessness, irritability of temper, and depression of spirits may also occur.

Chronic Gout.—With the progress of the disease, the acute exacerbations become more frequent and a larger number of joints become affected. The tarsal, ankle, knee, hand, and wrist joints are the ones most likely to be involved, in the order of frequency mentioned. The elbows, shoulders, and hips are more rarely attacked. The periarticular tissues become thickened, and densely infiltrated with biurates. The latter, particularly about the toe, knee, finger, and elbow joints, may give rise to large joint-tophi, which, in the case of the knee and elbow joints, may reach the size of a walnut. These tophi may cause striking knob-like deformities of the knuckle and interphalangeal articulations. They gradually become superficial, and appear whitish through the superimposed skin. The latter, especially over the knuckle and metatarsophalangeal joints, may become inflamed and actually ulcerate, and the contents of the tophi discharge as a whitish, chalky material, which, on microscopic examination, reveals the characteristic needle-shaped crystals of sodium biurate. In these cases of chronic "tophaceous" gout, the commonest situation for the tophi is the cartilage of the ear, in the region of the helix and antihelix. They appear first as slight reddish elevations in which, as time goes on, the biurate can be recognized with the naked eye as a whitish "chalk-stone like" deposit. The term "chalk-stone" is not altogether a misnomer, for Ebstein and Sprague have shown that tophi contain from 12 to 13 per cent. of calcium biurate, although the greater portion, 57 per cent., is composed of sodium biurate. Subcutaneous tophi may occur about the knees and along the extensor surfaces of the forearms, and may be mistaken for fibroid nodules. They

may also occur in the palms, and soles, and over the sacrum, and in the tendo Achillis. Tophi sometimes occur in the tarsal cartilages of the eye, in the sclerotics, and in the cartilage of the nose. The bursæ over the olecranon and patella may become inflamed and be the seat of sodium biurate deposition. Polyarticular attacks, with moderate fever reaching 101° F. occur with frequency, and in the intervals the unfortunate victim is not entirely free from pain, and always conscious of joint disability. Owing to the lessened amount of synovial fluid in these chronic cases, audible creaking of the joints may occur, and there is sometimes palpable crepitation. The acute joint exacerbations may be afebrile, a feature which should always lead the physician to suspect a gouty origin for the joint symptoms. The pulse tension is increased, the peripheral arteries become sclerosed, and hypertrophy of the left ventricle develops. Cramps of the calf, abdominal, and thoracic muscles may be most annoying. Digestive disturbances are common. The victim of chronic gout may possess marked mental and bodily vigor. Certain of the most distinguished members of our profession have been martyrs to the disease, notably the older Scaliger, Jerome Cardan, and Sydenham, whose statement that "more wise men than fools are victims of the affliction" still holds good. Although the subject of chronic gout is liable to be carried off by some terminal affection such as uremia, pleurisy, pericarditis, peritonitis, and meningitis, yet the victims not infrequently live to a good old age. The question has been much discussed as to whether Heberden's nodes ever occur in gout. Although of rare occurrence, it seems quite certain that they do occur, for Charcot, Duckworth, and Minkowski, have described them in cases of unquestioned gout. Dupuytren's contraction of the palmar fascia has been described.

Irregular Gout.—This comprises a nondescript group of symptoms which have usually been embraced under the terms *lithemia*, or a *uric acid*, *lithic acid*, or *gouty diathesis*. These irregular features are observed in members of gouty families who may never have suffered from an attack of gouty arthritis. They occur, also, in those who have eaten and drunk too freely, without taking sufficient exercise, and who have been fortunate enough to escape an acute attack. In families with marked hereditary predisposition, the daughters often escape, while one son may have gouty attacks of great severity even though he lives a temperate life and endeavors to avoid the conditions favoring the disorder. Another son, on the other hand, has only the irregular features, and never the acute articular affection. While the irregular manifestations are more likely to occur in inherited gout, they may also occur in the acquired form. There is an unfortunate tendency on the part of many physicians to ascribe certain obscure symptoms to a so-called uric acid diathesis, especially if they find a deposit of uric acid or urates in the urine, although there is often not a vestige of evidence to justify this view. There are certain health resorts in this country from which nearly every patient comes away imbued with the firm conviction that his blood is "filled with uric acid," and that this is responsible for his various nervous features. The patients are usually pleased with the explanation,

and it is a difficult task to disabuse their minds of the fallacy. Among the commonest manifestations of irregular gout are the following:

(a) *Cutaneous Eruptions*.—The most distinctive is eczema. The favorite seat is the external ear, but the inflammation may spread to the face, forehead, and back of the neck. It may be very obstinate, and even extend to other parts of the body in patients of advanced years. Symmetrical patches of psoriasis may occur on the legs. Attacks of herpes zoster have occasionally occurred. The nails are often striated and fluted, or lined vertically.

(b) *Alimentary Disorders*.—There may be psoriasis of the tongue. Notwithstanding numerous statements to the contrary, Duckworth asserts that no uratic deposits are met with in connection with the jaws, teeth, or gums. It has been held by some that the development of tartar on the teeth is a gouty manifestation. There seems no justification for this view. Some patients are subject to frequently recurring attacks of pharyngitis with great injection of the vessels. A gouty parotitis occasionally occurs. Attacks of what is termed biliousness, in which the tongue is furred, the breath foul, the bowels constipated, and the action of the liver torpid, are not uncommon in gouty persons.

(c) *Nervous Manifestations*.—Some of the most frequent manifestations of irregular gout come under this heading. Headaches and migraine attacks are common. Neuralgias are not uncommon. Sciatica is believed frequently to have a gouty basis. Duckworth has emphasized the occurrence of hot or itching feet at night. Plutarch mentions that Strabo called this symptom "the lisping of the gout." Cramps in the leg and abdominal muscles may be troublesome.

(d) *Urinary Disturbances*.—Many fallacious opinions have been formed by physicians concluding that a person is suffering from a uric acid diathesis by finding deposits of uric acid and urates in the urine. The solubility of the latter is dependent upon so many factors, important among them being the amount of urinary pigment and the percentage of the various salts, that it is entirely unjustifiable to draw any definite conclusions as to the quantity of uric acid excreted without making quantitative analyses. Uric acid precipitation may occur, although there may be actual diminution in the uric acid excretion in the twenty-four hours. Individuals with a gouty habit are undoubtedly prone to gravel, and to uric acid calculi. Duckworth points out that articular gout and calculi rarely coexist although they may alternate. Albuminuria is very common in the gouty dyscrasias. Oxaluria also occurs. Hematuria may occur in very old persons. Phosphatic gout has been described. It occurs without the articular features. Severe pain comes on in the night and there is spasmodic dysuria. Urethritis, with a purulent discharge, is said to occur either spontaneously or following a pure connection.

(e) *Ocular Manifestations*.—Hutchinson called attention to hot and itching eyeballs as a frequent sign of masked gout. Associated or alternating with this symptom there may be attacks of episcleral congestion. The writer observed repeated attacks of unilateral conjunc-

tivitis in a gouty patient, who for years had no articular symptoms. These would occur with, or independently of, a gouty pharyngitis.

(f) *Cardiac Manifestations*.—A peculiar paroxysmal disturbance of the circulation is sometimes witnessed, in which the heart-beats are very rapid and a condition is produced which Roberts termed the “run-away heart.” There may be attacks of cardiac pain without manifestations of cardiac disease.

(g) *Pulmonary Features*.—Greenhow has pointed out that persons of the gouty habit are liable to suffer from chronic bronchitis. Asthmatic paroxysms may also occur. The prevalence of emphysema is well recognized.

The Urine.—During the acute paroxysms the urine is scanty, high colored, and is generally stated to contain a deposit either of urates or uric acid. In the writer's experience in hospital work, such a deposit is the exception rather than the rule. There is usually a trace of albumin, and there may be a mild glycosuria. Careful search will usually show a few hyaline or granular casts. Quantitative analyses will always show a marked reduction in the amount of uric acid below the usual level for two or three days before the acute attack. Twenty-four or forty-eight hours after the onset of the acute symptoms the uric acid curve rises, and the amount may reach 0.7 to 1 gram, the upper limit for normal. As the acute symptoms subside, the curve falls to 0.4 gram, the lower limit for normal, or usually below this. In chronic gout, the urine is usually increased in quantity, pale, of low specific gravity, and always contains traces of albumin and hyaline and granular casts. Although some have failed to find a constant reduction of uric acid in the intervals between the acute attacks in these cases, the writer's analyses have practically always shown a very marked reduction, often not more than 0.1 or 0.2 gram being precipitated in the twenty-four hours. In one or two cases, he has failed to find, on certain days, any precipitation of uric acid as ammonium urate, with Folin's modification of the Hopkins quantitative method. Many hold that there is no corresponding increase in the excretion of the phosphoric acid with that of the uric acid during the acute attack, but, in some of the cases followed, the writer found a striking parallelism in the curves of the two acids. If the uric acid be derived from nuclein destruction a correspondence in the curves would rather be expected.

Complications.—Cardiovascular.—Arteriosclerosis is extremely common and, owing to the increased tension, hypertrophy of the left ventricle occurs. In due time this may give way to dilatation, causing palpitation, irregular heart action and eventually a condition of asystole. Myocarditis is very common in the obese cases. This is probably induced by the atheroma involving the coronary arteries, and may be the eventual cause of the patient's death. Owing to the coronary disease, anginal attacks may occur. A terminal pericarditis is not an uncommon event, but this is usually attributed to the renal lesion rather than directly to the gout itself. Aneurysm and apoplexy may occur. Phlebitis and venous thrombosis are well recognized as occasionally of gouty origin. The French are inclined to the view that many instances of so-called idiopathic thrombosis of the veins are due to a gouty dyscrasia.

Renal.—A chronic interstitial nephritis, and small granular kidneys, are almost invariably present in the chronic form of the disease, and the majority of gout patients die of uremia.

Retrocedent Gout.—This term is applied to a group of serious internal symptoms, occurring coincidently with a rapid disappearance, or improvement, of the joint manifestations. They may be so grave as to cause death, and may be considered among the complications of the disease. With a sudden cessation of the joint inflammation there may be severe gastro-intestinal symptoms—pain, vomiting, diarrhœa, and great depression, and death may occur during such an attack. On the other hand there may be cardiac manifestations—dyspnœa, precordial pain, and irregular heart action. Cerebral features, such as delirium, coma, or apoplexy, may occur, but in a majority of cases these symptoms are probably uremic.

Of the *eye* complications, an iritis is recognized as being of gouty origin. Glaucoma occurs. Hutchinson described a hemorrhagic retinitis. This may be of renal origin, but it is especially characterized by being unilateral, and affecting the left eye most frequently. A suppurative panophthalmitis has also been described.

Glycosuria and Diabetes.—Glycosuria is comparatively common in gout. It may, in certain cases, be dignified by the name of mild diabetes mellitus. It occurs, usually, in the obese gout patients. The glycosuria may alternate with arthritic manifestations (diabetes alternans). Lecorché observed 23 cases of transitory or permanent glycosuria in 150 cases of gout. The etiology of the glycosuria is difficult to explain, but Minkowski thinks that, owing to the prevalence of arteriosclerosis in gout, there may be sclerotic changes in the pancreas, corresponding to the arteriosclerotic diabetes described by Hoppe-Seyler and others.

Diagnosis.—In the majority of cases of the acute form no great difficulty should arise. The predilection for the local inflammation to attack the metatarsophalangeal and the tarsal joints is very characteristic. The marked reddening and the shiny appearance of the skin, together with the intensity of the pain, are extremely suggestive. Before the disease has definitely reached the chronic stage the joint inflammation may be polyarticular, and many of these cases are diagnosed as rheumatic fever. Careful inquiry regarding heredity, habits as to eating and drinking, together with the occupation, will often give the proper clue. The examination of the blood for an excess of uric acid is of value.

Quantitative determinations of the uric acid in the urine help us little, unless one is able to follow the curve, before, during and after an acute attack. A valuable procedure is the quantitative estimation of the uric acid in the urine, first on a purin-free and then after the addition of a known quantity of purin added to the diet. In a normal individual when some purin food is added, the excretion of the added purin is prompt, and is completed in two days; on the other hand, the gouty individual shows a delayed excretion of such added purin, the increased elimination of uric acid continuing from three to five days.

It is in the chronic form, with occasional acute exacerbations, that the correct nature of the arthritis is often overlooked. This is particularly

the case if tophi have not yet appeared; but many cases go begging for a diagnosis even when these are present, owing to the failure of the physician to search regularly for tophi in the ears in all cases of acute or chronic joint affections. The tophi are commonest in the cartilaginous portions of the ear in the vicinity of the helix and antihelix. They are usually small, superficial, and whitish in appearance. They may be more deeply seated and the biurate deposits may not be seen with the naked eye. Microscopic examination of the contents shows the characteristic needle-shaped, acicular crystals of sodium biurate. The presence of these crystals is pathognomonic of gout. Not to be confused with the tophi, are Woolner's tip or the Darwinian tubercle, which is more developed in some than in others, small fibroid nodules on the margin of the ear, and small sebaceous cysts. The latter is the only one to give rise to any real confusion, and the finding of oil droplets and epithelial cells, with the absence of biurate crystals in the contents, easily differentiates the two. Where there are large biurate accumulations about the toe, finger, knee, or elbow joints, the diagnosis is manifest at first sight. It must be recalled that subcutaneous tophi, clinically indistinguishable from rheumatic fibroid nodules, may occur over the extensor surfaces of the forearms and about the knees, and may, to the uninitiated, be confirmatory of a diagnosis of rheumatism. It is well in any such doubtful cases to excise one of these nodules and examine microscopically. The presence of sodium biurate deposits in them points definitely to gout. A feature of diagnostic importance is the fact that an attack of acute gouty arthritis may be afebrile. Any polyarthritis, with acute manifestations and unaccompanied by fever, should always cause a strong suspicion that it is gouty in origin. In these chronic cases, the habits of life and the history of the situations of the initial attack of arthritis are most important. If there be an arthritic family history, if the patient has indulged freely in fermented beverages, or has had an occupation subjecting him to possible lead infection, and if the initial or early attacks have been limited to the metatarsophalangeal or tarsal joints, the chances are strongly in favor of the disease being gout. The *x*-ray photograph may be of some assistance. Where there are periarticular deposits of biurates in considerable masses, these will be recognized as shadows in the photograph. Where this is the case one will be reasonably sure, without the photograph, that the periarticular thickening is due to biurate depositions. The weak feature in the diagnostic value of the *x*-rays, is that they are practically of no assistance in those cases in which they would be of the most value, namely, where the biurate deposits are limited to the articular cartilages. In these cases, the *x*-rays fail to reveal the existence of the deposition, either in the photographic plate or in the reproduction.

As our knowledge of chronic articular affections has increased, the opinion is becoming more firmly established that there is no such condition as "chronic articular rheumatism." An acute rheumatic arthritis, when it subsides, practically never leaves any deformity or limitation in functional activity. Consequently, when deformity or impaired motion supervenes upon one or more attacks of acute arthritis, we can

be reasonably certain that we are not dealing with a rheumatic affection, but rather with gout or arthritis deformans. It is with the latter affection that the greatest difficulty in the differential diagnosis is likely to occur. In *arthritis deformans* certain features aid us in the differentiation. In the case of deformities of the hands, there is a greater tendency to ulnar deflection of the fingers. A most important differential point is the almost constant occurrence of atrophy of the dorsal interossei muscles of the hands, producing a depressed appearance over the metacarpal region. Heberden's nodes point toward arthritis deformans, although they have been in rare instances described in cases of undoubted gout. The tendency of the laity, and also of many physicians, is to incorrectly consider these enlargements of the terminal finger-joints as a manifestation of gout. When the larger joints are involved in arthritis deformans, such as the knee, wrist, or elbow, the deformity is more likely to be of a fusiform shape with considerable muscular atrophy above and below. Needless to say, tophi do not occur in this disease. The x-rays are of undoubted value in differentiating the two affections when actual joint deformity has occurred. Osteophytic growths, or atrophy of the ends of the bones and of the joint surfaces, point respectively to the hypertrophic and atrophic forms of arthritis deformans. It should be recalled, however, that Wynne has described bony outgrowths about the joints in gout. The joint distortions of arthritis deformans are very common in women while those of gout are rare. The frequently used term "rheumatic gout" should be abandoned. The disease for which it stands has nothing to do with gout and should be called arthritis deformans.

A chronic arthritis, accompanied by marked arteriosclerosis and a urinary picture of chronic interstitial nephritis, should strongly suggest gout as its origin.

The diagnosis of the *irregular forms* of gout in which there have been no articular manifestations, often presents great difficulty and is subject to much uncertainty. The existence of a family history of gout is very important in arriving at the basal cause in these cases.

The writer's personal conviction is that gout in this country is much more prevalent than is generally supposed. Many cases of the acute, and particularly of the chronic, form are mistaken for rheumatism, owing to the failure of the physician to ascertain the family history, the patient's habits, the history of the early arthritic attacks, and to search for evidences of tophi in the ears or elsewhere. It is important to enter a protest against the tendency in certain quarters to ascribe nearly every obscure symptom, usually those of nervous or gastric origin, to a gouty diathesis. The idea that migraine attacks, accompanied though they may be by a precipitation of uric acid or urates in the urine, are due to uric acid dyscrasia, is based on evidence that is far from convincing.

Prognosis.—Once manifestations of gout have made their appearance, they are likely to recur at intervals throughout subsequent life. It occasionally happens, however, that a patient, who in earlier years has been subject to recurring attacks of arthritis, may never show any manifestations after the fiftieth or sixtieth year. This may, in part, be a result of treatment, particularly as regards the habits of living, but it

occasionally occurs spontaneously, without the aid of therapeutic measures. It is the latter fact that should make us rather conservative in drawing conclusions regarding the effect of any line of treatment. A fatal termination is unusual in the acute stages of the disease, although it may occur from the severity of the symptoms resulting from retrocedent or "metastatic" gout. The duration of life is not likely to be materially shortened, so long as the disease maintains its regular character with distinct arthritic manifestations. Often when these appear to play a much less prominent part in the gouty picture, visceral complications are likely to arise which may hasten the patient's death. The fatal termination in chronic gout cases is usually due to uremia, myocarditis with dilatation of the heart or to pericarditis. As we well know, the victims of regular gout often live to an advanced age.

Treatment.—Until we know with positive certainty the actual basal cause for gout, the treatment must necessarily be largely empirical. There is a steadily growing belief that the symptoms of gout are not directly traceable to the action of uric acid. The pathological findings indicate, however, that uric acid and its salts play a conspicuous part in the lesions. The various therapeutic measures have been directed mainly toward influencing purin metabolism, and particularly with the object in view of reducing the excess of uric acid in the blood. It is conceivable that this reduction may be brought about in one or more of the following ways: (1) diminishing the formation of uric acid; (2) increasing its elimination; (3) increasing the rapidity of its oxidation in the body; (4) increasing its solubility in the blood and tissue juices.

Prophylaxis in Members of Gouty Families.—In families in which there is a marked history of hereditary gout, something may be done to lessen the liability of individual members to develop active manifestation of the disease. By temperate living, abstaining from alcohol, and eating moderately, the risks are materially diminished. An active outdoor life, with plenty of exercise and regular hours, will do much to keep an inborn tendency to the disease in abeyance.

The treatment of the disease after actual manifestations have made their appearance may be discussed under various headings: hygienic, dietetic, alkalis and mineral waters, medicinal, local measures, and operative treatment.

Hygienic.—Gout prevails chiefly among well-to-do individuals who are not forced to make a livelihood by following occupations requiring even the average amount of physical exercise. Many manifest a tendency to obesity and frequently lead sedentary lives. It is most important in these persons to encourage a more active outdoor life requiring physical exercise in moderation. This must not be overdone, and must be confined within the limits of fatigue, for we know that an acute attack may be precipitated by excessive physical exertion. The patient should be encouraged to do a certain amount of walking each day, and a particularly useful exercise is horseback-riding, owing to the beneficial effect it has on the intestinal functions. Golf can be highly recommended, as it gets the patient into the open air, is not too violent, and commands a certain fascination for individuals of all ages. As an adjunct to outdoor

exercise, certain indoor gymnastics may be with advantage prescribed, such as the use of dumb-bells, Indian clubs, and the various forms of resistance movements. Massage will increase the muscular tone, stimulate the circulation, and tend to improve the general metabolic functions. The skin functions should be increased by systematic bathing. In the sthenic cases cold baths may be used, and, where there is a tendency to obesity, with no contra-indications in the way of valvular or myocardial disease, an occasional Turkish bath may be taken with advantage. The bowels should be carefully regulated. The patients should dress warmly, avoid rapid changes in temperature, and be careful not to have the skin suddenly chilled.

Dietetic.—The regulation of the food is undoubtedly the most important factor in the treatment. Meat is the article supposed to possess the most baneful influence, and over which there has been the most discussion. The red meats have for a long time been considered much more injurious than the white meats and fish. Kaufmann and Mohr have shown that there is very little difference between the two so far as the purin content is concerned. Von Noorden and Umber recommend the determination of the purin tolerance of each individual by giving, after several days of purin-free diet, a definite quantity of meat and noting how promptly the individual eliminates this purin. Von Noorden then permits each day as much purin as the individual has demonstrated himself capable of caring for. Umber, according to the delay in excretion, gives from one to six purin fast days each week to allow complete freeing of the system of excess of purins. This he continues for years and since it has been shown that uric acid retention is greatest at night, he advocates giving what purin is permitted early in the day. In undoubted cases of gout meats should be given in very small portions only once a day, and from time to time the patient should be put on a purin-free diet for several successive days.

The protein foods considered particularly injurious, are those rich in cell nuclei and, consequently, containing an abundance of purin bodies. These comprise the thymus, pancreas, liver, kidney, and brain. The meat extracts are to be avoided, owing to their richness in nitrogenous extractives and salt. Straus and Eitner found that the uric acid excretion was increased one to one and a half times after the giving of 50 grams—a very large dose—of Liebig's meat extract. Fresh fish may be permitted in moderation, but, weight for weight, it has been shown that they cause just as large a uric acid output as do meats. Salt fish should be avoided. Fish roe and caviar should be forbidden, owing to their richness in nuclein, although in the latter it is in the form of paranuclein.

Eggs constitute the most valuable protein food for gout patients, in that they are free from purin bodies. Milk, for the same reason, is also most useful. There is no scientific basis for the belief by some that cheese should be excluded from the diet. According to the analyses of Rosenfeld and Orgler, casein does not cause an increase in the uric acid excretion. Cheese may therefore be permitted in moderation.

Starchy foods may be freely allowed. An exclusive starch and vege-

table diet has its advocates still, but their number is gradually diminishing. Bread, rice, potatoes and other garden vegetables, may form a liberal portion of the dietary. Cucumbers and tomatoes had better be avoided. In Germany, particularly, the vegetable albumins have been used as a protein food, and as a partial substitute for bread in gout. Of these, aleuronat and roborat have been most extensively used.

Until recent years the prevailing belief has been that fruits were harmful. It was thought that the acids contained in the fruits were injurious. Since the time of Wohler, however, it has been held that the acid combinations in the fruits are oxidized in the system into carbonates and consequently fruit must be considered an alkaline nourishment. The best opinion at the present day favors the free use of fruits. The experience in any individual case is the best teacher in this regard, for certain fruits, such as bananas and strawberries, particularly the latter, may excite joint pains, and cause pharyngeal symptoms.

Fats, in the form of butter particularly, may be allowed with freedom; and butter in large quantities was advocated by Ebstein.

All highly seasoned foods should be forbidden. Pepper, paprika, and mustard should not be permitted in dressings. Their only injurious effect is through impairment of the digestive functions. Vinegar should be avoided. Sir William Roberts, who maintained that the sodium salts are injurious, in that they diminish the solubility of the urates and favor their deposition, advises strongly against the use of sodium chloride in the food. He recommended potassium chloride as a substitute.

It will be seen from the foregoing that the most diverse views have prevailed concerning the proper diet. No set rules can be laid down. The diet in each individual case must be carefully considered. In general terms it may be said that the protein foods, particularly those rich in nuclein or purin derivatives, should be limited but not excluded. The general conviction at the present day is that quantity plays a more important part than quality. The duty of the physician is to see that the patient does not overeat, and to keep his digestive functions in the best possible condition.

The majority of gout patients are better off without any alcoholic beverages. Individual experience soon teaches the victim that his general health is better and that he is freer from attacks by totally abstaining from alcohol. The fermented beverages are those most liable to occasion a lighting up of the arthritic manifestations. The mere indulgence in a glass of beer or wine not infrequently excites in a few hours, or even minutes, twinges of pain in the joints. When alcohol is indicated, as it sometimes is in the asthenic cases with cardiac symptoms, whisky or brandy may be prescribed and does least harm. On the other hand the richer wines, such as port, sherry, Madeira, champagne, and Burgundy, and strong ales and stout, are very likely to provoke symptoms. In Germany and England, where wine-drinking is commoner than in this country, there is a tendency to rather greater leniency in the use of wine, and the lighter forms, such as the Moselle wines, are permitted in moderation.

The general advice is that tea and coffee should be eliminated from the diet owing to the methylxanthins they contain.

The gout patient should be induced to drink freely of water, particularly on an empty stomach early in the morning and before the various meals. There is no positive proof that the drinking of water itself causes any material increase in the uric acid elimination, but experience has proved the beneficial effect of the procedure.

Alkalis and Mineral Waters.—Although alkalis have been very highly recommended on many sides in the treatment of gout, owing to their supposed effect in increasing the alkalinity of the blood and consequently rendering the contained uric acid combinations more soluble and more readily excreted, there has in recent years been a growing scepticism of their efficiency. Freudberg has shown that, in the doses in which they are usually given in gout, it is extremely doubtful whether the alkalinity of the blood is at all increased. A serious fallacy also arises from concluding that, because an alkaline salt increases the solubility of uric acid in a test-tube, it is also going to have the same effect in the circulating blood, where the medium is much more complex and where the uric acid combination is entirely different.

Since Garrod confirmed the observation of Lipowitz that lithium urate was very soluble in water, and, in 1858, first recommended the use of lithium carbonate in the treatment of the disease, the various lithium salts have been held in high favor. Lithium carbonate and lithium citrate, in an effervescing tablet of 5 grains, dissolved in a tumbler of water and administered 4 to 6 times daily, are still popular remedies. Potassium citrate, or carbonate, in 20 to 30 grain (gm. 1.3 to 2) doses 4 times daily, may be given. These various alkalis are undoubtedly beneficial, but it is generally conceded that their salutary action is due rather to the liberal quantities of water with which they are administered than to the drugs themselves.

Mineral waters have always played an important part in the treatment of gout. All forms may be said to be beneficial, but the good effects are due more to the water than to the contained salts. As Osler says, "Much of the humbuggery of the profession still lingers about mineral waters, more particularly about the so-called lithia waters."

The mineral springs best suited for gouty patients in this country are those of Saratoga, Bedford, and White Sulphur; in England, Buxton, Bath, and Strathpeffer; in France, Aix-les-Bains and Contrexéville; in Germany, the Sauerling spring of Carlsbad, Wildbad, and Hamburg. The drinking of water at home in large quantities, and on an empty stomach, is beneficial but not so much so as at one of these springs, where the accessories to the "cure" mean so much. It is now claimed for these spas that much of their efficiency is due to the radio-activity of the water. The modified diet, freedom from business worries and cares, regular hours, proper exercise, baths, douches, etc., are important adjuncts.

A considerable literature has grown up in the last five years concerning the *radium* treatment of gout. This agent has been used in various forms of arthritis, but the best results are obtained in gouty affections of the joint. It is conceded that the radium is most effective, when

inhaled in an emanatorium, although improvement has followed the drinking of radio-active waters and by administering baths in emanation containing waters.

Medicinal Management of the Acute Attack.—The patient should be kept in bed, where he is usually quite willing to remain, owing to the severity of the pain. A mild saline laxative should be administered at the outset. The affected joint, where conditions permit, as in the case of that of the big toe, should be elevated, and wrapped in thick layers of raw cotton surrounded by oiled silk. In this way the joint is protected and the wool acts as a poultice, inducing local sweating, and also swelling, which tends to relieve the acuteness of the pain. The use of warm or cold applications locally must depend entirely upon the relative relief experienced by the patient in any individual case. Local anodynes may be tried when the pain is severe. A lotion of laudanum and water in various proportions may be applied. Whisky and water, applied quite warm, is a favorite remedy. Ichthyol and lanolin, 10 grains to the ounce, may be tried. Blisters, and counter-irritation by the use of the cautery, are rather to be avoided, although the latter may give some relief. Some have claimed that the length of an attack may be much shortened by beginning early to induce motion of the joint by either active or passive means. Few subjects are willing, however, to consent to such heroic measures. Baking in the dry oven may ameliorate the pain. It is worth while to try the effect of passive hyperemia which in certain instances has given great relief.

Colchicum is the drug most likely to give relief from the pain. This is so prompt in many instances that it is often referred to as a specific, in much the same sense with which we use the word in connection with quinine and mercury. The drug may be administered either as the wine or the tincture of the seeds, preferably the former, in 20 minim (1 cc.) doses every two hours for 4 doses, and then every four hours until the pain is relieved, unless untoward effects manifest themselves. The relief to the pain is usually very prompt, but how it is effected is not at all well understood. It must be discontinued on alleviation of the pain because it is not known to have any direct action on the gouty process. Its active principle, colchicin, is also in use. The administration of colchicum may be abused and harm done. When given in excess, it causes vomiting, purgation, and cardiac depression. Colchicum sometimes fails to give relief and the salicylic acid preparations may be tried. Although not so likely to give early relief to the pain as in rheumatism, yet the salicylates, which were first recommended in gout by Germain Sée, are held in high repute by some clinicians. They are known to increase the total output of nitrogen and materially to augment the excretion of uric acid. It is not agreed, however, that their beneficial effect is due to this action. They may be given as sodium salicylate, oil of gaultheria, or aspirin. The last has gained favor, and has the advantage over the ordinary salicylates in being less injurious to the stomach. It may be given in 10 to 20 grain (gm. 0.6 to 1.3) doses every two or four hours, until pain is relieved. Antipyrine or phenacetin may be tried for the pain, but must be used with caution. In certain

cases when the pain is excruciating and does not yield to the usual remedies, a hypodermic injection of morphia should be administered. It is customary to give the patient alkalis during the acute attack, but their efficacy is doubtful. The citrate, acetate, or bicarbonate of potash, in 20 to 30 grain (gm. 1.3 to 2) doses every four hours, administered in large quantities of water, should be tried. Any benefit obtained is probably due rather to the water than to the alkali.

The diet is very important during the acute attack. It should be as purin-free as possible. A diet consisting of milk, eggs, butter, white bread, rice, sago, and cheese is free from nucleins. For the first day or two, when the fever is high, it is well to restrict the patient to milk and barley-water. As the acute symptoms gradually subside, eggs and other members of the above list may be added, and when the fever entirely disappears, small amounts of the white meats, such as chicken, etc., may be permitted.

When the acute symptoms have disappeared, gentle massage to the affected joint should be started, and active and passive motion encouraged. If the patient's means will permit, he should be sent to one of the mineral springs for a "cure," where the accessories are fully as important in the treatment as the drinking of the waters. Where this is not possible, a simple bitter tonic should be prescribed before meals. A common course to pursue is to give the patient a prescription containing 5 to 10 minims (0.3 to 0.6 cc.) of wine of colchicum with the same number of grains of potassium iodide, or 20 grains (gm. 1.3) of potassium acetate or citrate after each meal and at bedtime, for two or three weeks. The patient should be induced to drink freely of water before meals and on retiring, to restrain his appetite within reasonable bounds, and to indulge in some daily exercise.

In the last two years *atophan* (phenylquinolin-carboxylic acid) has been strongly advocated in gout. It is claimed that it lessens the pain in the acute attack and causes a marked increase in the uric acid elimination. It is extensively used in Germany and the writer has found considerable benefit from its use. The increase in the uric acid output may be due to destruction of tissue nucleoproteins. It is given in 7.5 grain (0.5 gram) doses 4 to 6 times in the twenty-four hours.

The Uric Acid Solvents.—Hardly a year passes without one of these much vaunted remedies being introduced to the medical profession. They almost invariably fail to justify the claims made for them. Just as in the case of the alkalis, this is due to these solvents failing to act in a complicated medium like the blood-serum as they do in a test-tube.

Piperazin, lycetol, lysidin, urotropin, urea and urol have all been advocated as uric acid solvents, but all of them have proved failures. Any possible benefit resulting from their use must be attributed more to the fact that patients can be induced to drink more water in this way.

Remedies to Increase the Rapidity of Uric Acid Oxidation.—*Oxygen inhalations* have been tried, but the analyses of Honigsmann and Krafft show that there is no diminution of the uric acid excretion, and no evidence to point toward its increased oxidation in the system. Thyroid tablets and spermin have been used for the same purpose, and with the

same results. From what is known concerning the action of various enzymes in transforming the various purin bases one into another, and of the action of a special oxidase in destroying uric acid, we may hope that some means may yet be discovered to influence their action.

Operative Procedures.—It occasionally happens that surgical measures are indicated. When joint tophi become inflamed, and spontaneously open and discharge biurates, a persistent discharging sinus may result. In these cases eradication of the tophus is advisable. The bursæ sometimes become inflamed, swollen, and painful, and, in some instances, free opening of them gives great relief. Riedel operated on two cases with gouty arthritis limited to one of the great toe-joints. A mistaken diagnosis was made in both instances, the arthritis being thought to be due to a suppurative process. At operation it was found that the arthritis was of gouty origin. The joint capsule was completely removed without interfering with the bone, and the edges of the operation incision were brought together without the use of sutures. In both instances the patients lived for years with no recurrence of arthritic attacks, death resulting from other causes. On the basis of these cases, Riedel recommends the ablation of the capsular tissues in those instances in which the arthritis has been confined to a single joint. On such limited experience, it does not do to draw any definite conclusions as to the advisability of operative procedures. The removal of the affected joint cannot eradicate the metabolic disturbance causing the disease. Further, we know that patients often go for years without recurrences of the arthritis.

As to the use of *electricity* it may be noted that Remak and Benedikt claim to have obtained good results by the use of the constant current locally applied to the affected joint, both in the acute and chronic form. Labatut, Jourdanet, and Levison, have reported beneficial results by the use of electrical endosmosis, or kataphoresis, with lithion, in the treatment of the joints and skin tophi. The galvanic current, with the electrodes moistened with a concentrated solution of lithion chloride, or carbonate, is passed through the affected joint or tophus, or is given in the form of an electric lithion bath.

General Management of the Chronic Cases.—The regulation of the diet stands first in importance. It is generally agreed that reduction of the total food intake is of more importance than the special restriction of any one of the three varieties of foodstuffs. In the case of the proteins, those that are most easily digested, such as eggs, fish, and the white meats, are preferable. Those rich in nuclein, such as sweetbreads, kidneys, liver, and brain, should be avoided. If any change be made, the vegetables should be increased at the expense of the proteins. The patient should be regular in his meals.

Plenty of exercise, of the character already outlined, should be taken. Worry, and all unnecessary psychical disturbance, must be avoided. In the case of podagra, special care must be taken to secure a properly fitting shoe. The individual should be warmly clad. The digestion should be looked after, and any tendency to constipation counteracted.

The majority of patients do not require anything medicinally, excepting during the acute exacerbations. They must be persuaded to drink

several glasses of water daily on an empty stomach. As it is difficult to get patients to do this, the object can be more easily secured by having them take some alkali, such as a 5-grain tablet of effervescent carbonate or citrate of lithia dissolved in a glass of water, several times daily.

Where the patient's means will permit, it is well to send him to one of the mineral springs for a few weeks' "cure" each year, where the accessories of the cure mean as much as the drinking of the water itself.

Treatment of the Complications.—In cases complicated by *diabetes* the carbohydrates should be restricted. The glycosuria is of a mild type and generally yields readily to dietetic treatment.

Where there are evidences of a serious *nephritis*, the proteins should be partially cut down. If uremic manifestations supervene, as they often do, the usual measures for this complication should be tried.

In the cases with an increasing tendency to *obesity*, the fats and carbohydrates should be cut down, and proteins permitted in larger amounts than would be allowed in the average case.

The *cardiac complications* require special attention. In the cases with evidences of myocardial weakness, the usual cardiac stimulants and tonics are indicated. If the condition be not a too serious one, and the patient's circumstances permit, a course of baths at the Nauheim Springs, in Germany, may help the cardiac features, and will also tend to alleviate the ordinary gouty symptoms. Still, the writer knows of patients with cardiac disease who have actually been injured by this treatment and feels that the greatest caution must be used in advising it.

CHAPTER XIX

OBESITY

By JAMES M. ANDERS, M.D.

Synonyms.—Lipomatosis Universalis; Adiposity; Corpulency; Fatness.

Definition.—Obesity is a metabolic disorder, commonly assuming the form of hypernutrition, and characterized anatomically by an excessive amount of bodily fat; it assumes clinical importance when the fat deposits throughout the body become burdensome or produce impairment of the functions, as shown by disinclination to muscular exercise, palpitation, dyspnoea, and other features. The condition is associated with, and dependent on, a variety of underlying affections; so that it may be rightly regarded as a symptom rather than a pathological entity.

Varieties.—Two leading forms are recognized: the plethoric and the anemic. These may merge into a third, or hydremic, form, and there are many transitions between the two typical varieties. The anemic variety reaches the hydremic stage much earlier than the plethoric, and, according to personal experience and observation, only a fragment of the cases composing the plethoric group merge into the terminal stage of the disorder. A division of the cases of obesity into general and local should also be attempted in practice (*vide infra*).

Etiology.—**Predisposing Causes.**—*Heredity.*—This was clearly traceable in 330 (or 60.7 per cent.) of 543 cases occurring in the writer's experience, and in some instances, through several generations; it cannot be said to depend upon the indolence of ancestors so much as upon peculiarities of the digestive and assimilative powers. In this group, a history of gout or in actual association with the obesity is common as in 235 (or 43.2 per cent.) of this series of 543 cases. "Rheumatism" was present in 104 (or 35.5 per cent.) of the cases. These figures indicate a close and vital connection between gout ("rheumatism") and obesity. In general terms, it may be said that gouty subjects, in whom a moderate degree of obesity is frequently associated, manifest a reduced oxidizing energy, as evidenced by a low hemoglobin content of the erythrocytes. In many instances of the sort the red corpuscles are normal or even increased, while the hemoglobin percentage may be as low as 70. Again, granted that a preformed fatty tissue exists as an independent organ, inherited qualitative peculiarities would account for the predisposition to an abnormal accumulation of fat in some cases at least. This view is supported by the fact that the parts showing normally the largest fat deposits, are primarily those in which excessive or abnormal accumulations principally occur.

Hereditary predisposition usually manifests itself early in life, but it may not show itself until a later period or until some exciting cause becomes operative. An inherited taint is more commonly observed

in females than males. Atavism may occur. With Kisch, Oertel, and others, the writer agrees that heredity is not more pronounced in the same sex (*e. g.*, from father to son, and mother to daughter), since his collective investigations tend to disprove this claim.

Age.—The general tendency to an abnormal accumulation of fat is more pronounced at certain periods of life than others; but this variability may not be dependent on the age *per se*, inasmuch as it is difficult to dissociate the influence of habit, alimentation, and other factors. In young infants, a marked degree of obesity may occur, and in many cases it is principally ascribable to the milk and farinaceous articles of food in the diet. This form of infantile corpulency is apt to disappear subsequently. On the other hand, in a certain proportion of the cases of obesity commencing at birth, a slow and gradual increase in the amount of fatty tissue may take place during childhood and adolescence. In the majority of instances, however, corpulency develops later in life, in the male during the period between forty and fifty years, and in the female during the two decades between thirty and fifty years. The favoring influence of puberty apart, during adolescence, a period of life in which enormous quantities of nutritive material are demanded by the organism, the tendency is toward a decrease of adipose tissue. Again, in advanced years, when retrograde metabolic processes occur, favorable conditions are missing.

Sex.—Obesity, under normal conditions of life, is more common by far in the female than in the male. Personal experience and observations confirm the view that, owing to the lower percentage of hemoglobin in women in comparison with men, the oxidizing energy is correspondingly diminished, and hence a greater tendency to transformation of the carbohydrates into fat. The condition dated from the puerperium in 16.2 per cent. of the writer's series in females, and from miscarriage in 5.3 per cent. In multipara, each subsequent pregnancy increased the general tendency to obesity, in some cases at least.

Other factors expressly favorable to the development of an abnormal amount of fat in the female are: the more quiet, inactive life, the greater tendency to indulgence in fat-forming articles of diet, puberty, and the menopause (slight). With reference to the menopause, Tilt's statistics are significant: Of 382 cases, 121 had grown heavier, 171 had retained their former weight, while 90 had become lighter. When the menopause leads to greater corpulence it is manifested especially by the acquisition of an *embonpoint*. While the anemic type of the disease is more common in the chlorotic female, more cases of the plethoric type are met with in the male.

Temperament, Occupation, and Enforced Rest.—The indolent, sluggish, luxury- and rest-loving, phlegmatic individual is disposed to corpulency. This fact explains why obesity is so commonly observed among certain races—southern Italians, Orientals, South Pacific Islanders, Dutchmen, and certain African races. Similarly the inhabitants of low countries of the temperate and arctic regions are prone to abnormal fat-deposition. Phlegmatic persons are inclined to consume large quantities of fat-forming substances.

The *occupation* may exert no inconsiderable effect, a sedentary life favoring the development of corpulency. Any calling in which the required muscular activity is at a minimum predisposes to adiposity. The condition often dates from longer or shorter periods of enforced rest—*e. g.*, following accidents and illness. Following such acute infectious diseases as typhoid fever, pneumonia, and the like, adiposity, especially of the anemic form, not uncommonly develops. The writer's notes indicate that out of a total of 543 cases, 43 (or 7.9 per cent.) followed an acute illness. Among incidental predisposing causes are congenital anomalies and monstrosities (idiots, cretins, acephali).

Exciting Causes.—Obesity is especially dependent on the habitual ingestion of abnormally large amounts of fat-making food, and the intemperate use of alcoholic beverages—sweet wines, beer, ale, and porter, in particular—with or without deficient exercise. The source of the fat is considered to be the fats and carbohydrates taken as food, although probably it is derived to a considerable extent also from the albuminoids, as seen in the method of treating cases of tuberculosis with milk and raw eggs. An excessive diet of starches and sugars acts indirectly as a fat-producer by lessening the oxidation of the fats and proteins which may be ingested, because the carbohydrates themselves are so readily oxidized. Hence, excessive indulgence in any one of the several varieties of diet may produce the condition.

Intemperance in the use of *alcohol* plays an important role by inducing hypernutrition. Alcohol is readily oxidized thus allowing the fat previously present to remain undisturbed. Alcohol also prevents tissue-waste; and finally, certain beverages, as beer, contain starches in considerable amount. It has been estimated that a person taking habitually 5 or 6 glasses of beer daily, would consume $5\frac{1}{4}$ ozs. (150 gm.) of starch, or about one-half of the required amount, in the same period. The intemperate man, on account of physical torpor which is the necessary result of his habits, is disinclined to muscular exercise. Familiar illustrations in this regard are afforded by inn-keepers, brewers, and the inhabitants of certain countries, like Germany and Bavaria.

Special Pathology.—The most obvious change is the decided increase in the adipose tissue throughout the body. The fat deposits are most marked in localities in which fatty tissue is normally present, as under the skin, in the panniculus adiposus, and the mammary regions; they also occur in the various internal organs and tissues that are altogether, or almost, free from fat in healthy individuals. The physiological amount of fat has been estimated by Beclard and Quesnay at no more than 5 to 6 per cent. of the whole weight in adults, while the proportion of fat in the newborn varies between 9 and 18 per cent. The normal fluctuations are greater in women (to whom the higher figures also pertain) than in men, and a moderate increase of fat beyond the percentages given above, after the fiftieth year, may be regarded as physiological. The variations in the amount of fat within the limits of health are dependent on age, climate, and family and racial characteristics.

The deposition of fat which always occurs in the connective tissue greatly increases the bulk or dimensions of the body. The round face,

"double chin," bulky, deep chest, large waist, conspicuous and sometimes pendulous abdomen, and short, thick, cylindrical limbs, are familiar. Children may be obese, and the disorder is rarely congenital. It is to be observed that corpulency, "fatty infiltration," and "fatty degeneration," are not synonymous terms.

The various viscera, more particularly the *heart*, are overlaid with fat, and the interstitial connective tissue may be the seat of fatty infiltration. Out of 103 cases, lasting for periods ranging from a few to many years, of extreme adiposity that have occurred in the writer's experience, 5 cases gave clinical proof of the existence of true fatty infiltration.¹ This morbid process (infiltration) is limited to a thin layer of the inter-muscular fibrous tissue, situated directly beneath the epicardium, and is not to be confounded with true fatty infiltration.

Hypertrophic dilatation of the heart is frequently present in high degrees of plethoric adiposity, owing to an enlarged volume of blood, and the arteries may show fatty changes in the intima and media, and later those of arteriosclerosis. The arterial changes may lead to the development of chronic interstitial nephritis, which thus becomes a late complication of obesity. The *veins* are often the seat of larger or smaller varicosities. The *kidneys* and *lungs* may be enlarged owing to fat deposits and fatty infiltration. Additionally, passive congestion and œdema of the lungs, secondary to the cardiac weakness, may be found at autopsy. Of the viscera, the *liver* alone is the seat of normal fat deposits, but in obesity these accumulations may cause enlargement of the organ. The *stomach* may be dilated, and a catarrhal gastritis and enteritis are sometimes observed.

Pathogenesis.—Fats conserve the albumin in metabolism by furnishing heat and force during their combustion—an important chemico-physiological function. By thus favorably affecting the metabolic processes, they at once rise to an important position in connection with the general nutrition. The origin or mode of formation of the excessive fat accumulations is a subject that is imperfectly understood. In the plethoric form, obesity most probably results from the ingestion of an excessive amount of fat-producing carbohydrates and their complete transformation, owing to an abnormally active digestion and assimilation. *Per contra*, in the anemic variety a deficiency in the oxidizing power of the system may be assumed to exist and constitute the principal factor. Under these circumstances, a normal proportion of carbohydrates in the aliment used will fail to be destroyed on account of deficient oxidation. Obesity, therefore, may be said to be dependent on disturbance of cell-activity; and the overuse of carbohydrates leads oftentimes directly to an excessive manufacture of fats. The liberal consumption of proteins may also result in a fat-forming residue, which, if not destroyed by oxidation, may produce adiposity. The disturbance of the metabolic processes may be transmitted through heredity.

Histology.—Microscopically, differences in the size and number of the fat globules are exhibited. Thus, in the plethoric form of polysarcia the

¹ *Amer. Jour. Med. Sci.*, 1901.

fat globules are large, being distended with droplets of fat; their cell envelope and nuclei, however, are quite indistinct. When numerous, the fat vesicles are closely packed and their surfaces are faceted by mutual pressure. In cases of the anemic or hydremic variety in which the fat masses are soft and doughy to the feel, the cells are less completely filled, and the cell membrane and nucleus are easily distinguishable.

The process of fatty infiltration begins with the appearance of a small droplet within the cell envelope; this grows larger until "the cytoplasm forms a mere capsule about it and the nucleus is crowded and flattened in consequence." Microscopic sections, stained in the usual manner, do not show the presence of fat globules, but in the spaces previously occupied by them vacuoles are seen.

Symptoms.—Owing to the insidiously progressive character of the affection, and the absence of all characteristic prodromes, it is exceedingly difficult to fix the date of the onset as a clinical entity. At first, slight inconvenience, a sense of burdensomeness, and dyspnoea during walking or working, are the principal subjective manifestations, and, indeed, no other symptoms may be complained of for years. Later, with the slow and gradual development of the disease, and involvement of the various viscera, both the number and intensity of the clinical features are increased. Marked breathlessness on exertion, due to the hampering of the action of the heart and lungs by massive chest walls, fat overgrowth and the upward crowded diaphragm, are among the earliest conspicuous features. The symptoms presented by individual patients will vary according to the stage at which they come under observation. The two typical forms, anemic and plethoric, demand separate consideration.

1. **Plethoric Form.**—In this variety there is hypernutrition of all the tissues. Such patients often partake of large quantities of beer or other fluid during meals and the appetite is abnormally keen. In addition to the excess of fat, which is symmetrically distributed throughout the body, as a rule, the muscles, including those of the myocardium, are vigorous and voluminous. The blood shows a condition of abnormal richness both in erythrocytes and hemoglobin. In a number of patients the erythrocytes are over 6,000,000 and the hemoglobin over 110 per cent. The blood shows an increase in specific gravity, fluctuating, however, between 1.062 and 1.070, and that of the serum between 1.032 and 1.035.

Physical Signs.—The complexion is florid, the skin soft, smooth and in some cases the face looks congested; the lips, conjunctivæ, and other mucous membranes present a rosy hue. The neck is massive, the abdomen prominent, and the girth decidedly increased. The sweat glands are unusually active. But though the systole is abnormally strong, the impulse is felt indistinctly on account of fatty overgrowth and the subcutaneous fat. Later, as the result of myocardial weakness, and often before this in extreme cases, the impulse may be lost, both to inspection and palpation. The pulse is slow and of high tension; this causes arteriosclerosis with its usual consequences—dyspnoea, chronic interstitial nephritis, anginal seizures, and finally apoplexy. The vigorous contractions of the heart, due to muscular overgrowth, sooner or later grow feeble as the result of cardiac failure, the pulse

declines in fulness and volume and finally becomes small and arrhythmic. Bradycardia is not infrequent.

Indications of cardiac enlargement are present. In well-marked corpulency, however, it is always difficult, and sometimes impossible, to establish the boundary lines of dulness by percussion. The heart sounds remain clear for a long period, but with the progressive development of the condition become indistinct. Murmurs may be audible, most commonly in the aortic zone; they are probably not due to chronic valvulitis, but to either a roughened condition of the intima of the aorta or to relative incompetency. Again, the bruit may rarely be hemic in origin or "due to an abnormal, relaxed state of the heart muscle, or to weakness or insufficiency of the papillary muscles."¹ In advanced cases, arteriosclerosis, affecting particularly the aortic arch and the coronaries, is an associated lesion of comparative frequency.

The subject of obesity does not resist well the inroads of the acute infections, and his fat-laden viscera are likely to show degenerative changes at a premature period of life.

In another group belonging to this variety, the condition, if unchecked, leads to a marked increase of the general bulk of the body and various grotesque malformations. The features are broad and coarse, and some of the facial lineaments are obliterated. Indeed, the natural folds of the skin everywhere may be substituted by those formed of huge layers of fat. The fat deposits are most prominent about the neck, and the double and triple chin occur, also over the trunk and particularly the abdomen, which may be markedly pendulous. The maximum weight among the writer's patients was 412 pounds, and Weinberger observed a boy, aged ten years, weighing 266 pounds. At last locomotion may be impossible, partly from the increasing weight of the fat and partly from the extreme feebleness of the tissues, particularly those of the heart.

In some cases the muscular power diminishes rapidly, the appetite fails, profuse sweatings occur, and signs of general venous stasis may be observed. In the majority, however, venous engorgement develops more insidiously. Cough, distress of respiration, and asthmatic seizures, especially at night, signal the passive hyperemia of the respiratory mucous membrane. The symptoms of a gastric catarrh, dependent on stasis in the mucous membrane of the stomach, are in evidence, and with these the characteristic features of gastrectasis may be combined. Great thirst and bulimia may be observed in some cases at least. From analogous changes in the intestines, there is often constipation which may alternate occasionally with diarrhœa. The passive congestion of the kidneys is shown by a tendency to oliguria with albuminuria, and the presence of hyaline and a few granular casts.

As elsewhere stated, the poisonous products of tissue-metabolism are not eliminated in the normal ratio. Indeed, the writer has found that the daily renal output may be diminished one-half while the amount of food ingested is plus. Sexual desire is in abeyance and azoöspemia is not uncommon.

¹ See Schroetten, *Ziemssen's Hand-book*, §, 26.

In the last stage of the plethoric kind of obesity, malleolar œdema merging into progressive dropsy may arise and lead to a fatal end. Death may also come suddenly from cardiac paralysis.

2. Anemic Form.—This leading type, occurring usually in women, is characterized by and dependent on anemia, often of chlorotic type. Cases of the plethoric form rarely merge into this variety. The fatty depositions do not reach the gigantic proportions in anemic obesity of the opposite variety. Muscular exercise is difficult and early induces exhaustion, accompanied by distress of breathing and cardiac palpitation.

The symptoms are in a measure those characterizing the anemias in general, together with a peculiarly marked increase of fatty depositions in the usual places of predilection. The writer has the records of a blood examination in nineteen cases. In the majority of the instances the blood changes were of the chlorotic type. The hemoglobin percentage varied greatly—from 33 to 83 per cent.—the average being about 70 per cent. In about 35 per cent. of the cases, however, the erythrocytes and hemoglobin were reduced about equally. More or less poikilocytosis was commonly found; and also an occasional normoblast and a considerable leukocytosis (the count ranging from 11,000 to 31,000 per cmm.) was present in about 25 per cent. of the cases.

The *physical signs* are at variance with those found in the plethoric form. Inspection shows pallor of the bodily surface and the visible mucous membrane. The skin is inclined to free perspiration, and, in advanced cases may become wrinkled. "The skin is often irritated (intertrigo) by the excessive sweating, and by the friction of cutaneous surfaces in the folds of fat, as under the breast, at the abdominal and inguinal folds, and around the scrotum and labia. This may be followed by eczema." To the feel, the subcutaneous fat-cushions are soft and flabby and the muscles are lacking in firmness and strength. The signs of cardiac insufficiency become more or less conspicuous with the progress of the condition, and at last, as the result of falling arterial pressure, dropsy supervenes. Characteristic hemic murmurs are often heard.

While it is generally conceded that the principal factor in the production of this form of obesity is the feeble oxidation resulting from the greatly reduced hemoglobin-content of the erythrocytes, it may also arise from habitual muscular inactivity with insufficient nourishment. Obesity often originates in an attack of chlorosis during the "teens." It is probable that recovery in many chlorotic females is incomplete, and thus the foundation is laid for the future development of the anemic type of corpulency. In such instances the menses may be both scanty and irregular, and dysmenorrhœa may form the burden of complaint.

The appetite is impaired and capricious; in most cases carbohydrates are preferred to proteins. The tongue is furred and the breath often foul. Intestinal flatulence with more or less constipation is the general rule. The daily quantity of urine voided is small, due to diminished arterial pressure. Slight albuminuria is often found and is to be ascribed to passive congestion in the majority of instances, since, with improved tonus of the circulation as the result of the use of cardiac stimulants,

the albumin usually disappears. Attacks of intercurrent diseases are badly borne.

Complications and Sequelæ.—Among the principal complications, often the precursors of the terminal stage, are bronchitis, pulmonary congestion, anginal attacks, dyspnœa, hernia, albuminuria, glycosuria, arteriosclerosis, œdema, cerebral hemorrhage, and Cheyne-Stokes respiration. The dyspnœa, which is sometimes troublesome, is dependent on pulmonary congestion as the result of "light" breathing and feeble heart action during sleep. The writer has seen the vascular tension apparently increased, due to stimulation of the vasoconstrictors. Severe attacks of angina are also observed. Fatty infiltration may occur as a sequel, but it is extremely rare.

Circumscribed Obesity.—In many cases the fat-depositions are not distributed regularly over the entire body, but are confined to circumscribed portions—for example, the abdominal parietes, the mammary regions, and the hips. In other patients the fat-content is in excess in the trunk. Williams¹ points out that localized superfluous fat-deposits are due to lack of exercise of the underlying muscles, and attributes the "abdomenia figure" to insufficient exercise of the muscles of the abdomen. The causes for the localization of the depositions of fat in certain portions of the body are difficult to determine. The increased thickness of the fatty layer in the abdominal wall may be due to multiple pregnancies.

Diagnosis.—This is not difficult in the majority of instances, but it should include the particular variety of obesity present—for example, whether anemic or plethoric. Care must also be exercised in detecting associated conditions, as gout, anasarca, arteriosclerosis, and the like; also the complications and sequelæ. Myxœdema should not be mistaken for obesity, but this mistake has occurred. In both affections the general bulk of the body is greatly increased, but in myxœdema the skin is thick, firm, and inelastic; it is dry and rough and the facial lines of expression are obliterated. Again, in the latter disease the physiognomy is altered to a remarkable extent, while the lips, tongue, nostrils, and mouth, are all thickened by infiltration.

Prognosis.—This depends principally upon the degree, variety, and prevailing complications of each individual case. In the earlier stages of the plethoric type, in which the ingestion of too much fat-making food is the principal cause, the outlook is positively favorable under appropriate treatment. In more advanced cases, with associated arteriosclerosis, particularly of the coronaries, stenocardia, and œdema, the prognosis may be of the utmost gravity. On the whole, it is less favorable in the anemic or hydremic form than in the plethoric. Many of the former variety, however, are curable in proportion to the removability of the cause—the anemia. The tendency to relapse in all cases, even those in which an apparent cure has been effected, must be recollected. Medical officers of life assurance companies recognize obesity as an indication of impaired health, and when the body weight is decidedly

¹ "Some Aspects of Obesity," *Practitioner*, May, 1904.

disproportionate to the height of the individual, the risk is usually declined. When physical exertion induces early breathlessness, thoracic oppression, and palpitation, and the pulse becomes small ("thready") and irregular, the outlook is gloomy.

Modes of Death.—Among the commoner causes of death are: angina pectoris (from involvement of the coronaries), apoplexy, syncope, uremia, cardiac dilatation, intercurrent acute infections, and necessary major operations. Of the rarer modes of death may be mentioned rupture of the heart, cerebral thrombosis, hemorrhagic infarctions, carbuncles (to which subjects of obesity are liable), and pulmonary congestion or cedema.

Treatment.—Prophylaxis.—A child of a mother suffering from anemic obesity should be nourished by a suitable wet-nurse who is not predisposed by heredity to this form of obesity. In the earlier years of persons showing an hereditary disposition to corpulence, the fat-forming (farinaceous) substances must be greatly restricted in the dietary. The proportions of fat and protein allowed will depend upon the amount of muscular activity. Physical exercise should be advised and encouraged, but it is to be carefully regulated. Cool bathing is a useful prophylactic measure if carried on systematically and regularly. If anemia be associated during childhood, suitable forms of iron should be administered. At middle life, in those disposed to corpulency, all imprudences in eating and drinking should be avoided, and the quantities of various articles of food and the time of eating regulated. Outdoor sports and gymnastics should be also gauged accordingly. Prophylactic measures, however, must have reference to the special indications presented by individual cases. For example, the inclination to corpulency may be overcome by instituting measures preventive of the development of gout.

The treatment of confirmed obesity may be conveniently discussed under three heads: (a) the dietetic treatment; (b) the mechanical management (to increase oxidation); (c) the medicinal measures. There are few diseases that the physician is called upon to treat in which it is so vitally important to adapt the treatment to special cases as in obesity and it must be varied from day to day to respond to indications as they arise. If the dominating etiological influence is removable, this should be accomplished in the first instance and then attention given to the minor factors. Cases that present complications of various kinds may prohibit the exercise of the rule mentioned above. In well-marked cases in plethoric patients and in the anemic type, a more complex group of indications is presented, and usually two of the elements of treatment indicated above, (a) and (b), are prime requisites. Finally, that method must be selected which invigorates rather than weakens the patient.

Dietetic Treatment.—This is all-important. Broadly speaking, the principal variation from the ordinary dietary consists in a restriction of the fat-forming food, or carbohydrates. The carbohydrates should not be totally withdrawn, since the ingestion of large amounts of protein foods, which are difficult of complete metamorphosis, may excite digestive disturbances, gouty manifestations, and even chronic interstitial nephritis. It is the writer's almost invariable custom to allow

a limited proportion both of carbohydrates and fat, and thus accomplish two objects: (1) a slow consumption of the previous fat-depositions; (2) maintenance of the normal metabolic processes.

The principal systems of dietary are known by the names of Banting, Ebstein, and Oertel. In so-called "Bantingism," sugars, fats, and starches are greatly restricted in the dietary; water, however, is not reduced, and wines and spirituous liquors are allowed. Sir Dyce Duckworth has well said that as a system "Bantingism" is both unphysiological and impractical. In subjects of a rheumatic or gouty diathesis Banting's heavy protein and alcohol dietary is contra-indicated.

In Ebstein's diet-list the proteins are diminished, and carbohydrates greatly restricted, while fat is freely permitted. It is assumed that fat does not increase stored fat, and being less readily oxidized than the carbohydrates, it interferes less with the protein metabolism. Saccharine matter and potatoes are strictly forbidden. The following is an illustration of Ebstein's dietary:

Breakfast, 6 A.M. in summer, 7.30 A.M. in winter.—White bread, well toasted (rather less than 2 ounces), and well covered with butter. Tea, without milk or sugar, 8 or 9 ounces.

Dinner, 2 P.M.—Soup made with beef marrow. Fat meat, with fat sauce, 4 to 5 ounces. A moderate quantity of asparagus, spinach, cabbage, peas, or beans. Two or three glasses of light white wine. After the meal, a large cup of tea without milk or sugar.

Supper, 7.30 P.M.—An egg, a little roast meat, with fat. About an ounce of bread, well covered with butter. A large cup of tea, without milk or sugar.

The Oertel method is especially adapted for some cases of obesity with feeble hearts. This author allows more fat than Banting, but less fat and more (about double the quantity) proteins and carbohydrates than Ebstein. The amount of *free* water permitted daily is only one pint; about one pint additional in other food is allowable. His diet-table for obesity is appended:

	Albumin.	Fat.	Carbohydrates.	Calories.
Minimum . . .	156	25	75	1180
Maximum . . .	170	45	120	1608

Oertel also offers a special diet list in circulatory disturbances which comprises three parts:

1. The reduction of the amount of liquid taken with meals and during the intervals, the total for each day being 36 ounces (1064 cc.). Frequent bathing (including the Turkish bath in suitable instances) and pilocarpine are employed to promote free diaphoresis.

2. The diet is composed largely of proteins, as follows:

Morning.—A cup of coffee or tea, with a little milk—about 6 ounces (178 cc.) altogether; bread, 3 ounces (93 cc.).

Noon.—Three to 4 ounces (90 cc. to 120 cc.) of soup; 7 to 8 ounces (218 cc. to 248 cc.) of roast beef, veal, game, or poultry; salad or a light vegetable; a little fish; 1 ounce (32 cc.) of bread or farinaceous pudding; 3 to 6 ounces (93 cc. to 186 cc.) of fruit for dessert. No liquids at this meal, as a rule; but in hot weather 6 ounces (178 cc.) of light wine may be taken.

Afternoon.—Six ounces (178 cc.) of coffee or tea, with as much water. An ounce of bread as an indulgence.

Evening.—One or two soft-boiled eggs, 1 ounce (32 cc.) of bread, perhaps a small slice of cheese, a little salad, and fruit; 6 to 8 ounces (178 cc. to 236 cc.) of wine, with 4 or 5 ounces (120 cc. to 148 cc.) of water (Yeo)

3. Graduated exercise, as walking, the distance to be undertaken each day to be carefully specified and frequently, though gradually, increased. A like plan is to be pursued with reference to the degree of inclination. This invigorates the heart muscle. The Oertel method has gained an enviable reputation in Europe where special sanatoriums for its administration have been established. At these "Terrain curorte" are to be found, "health paths" of four different grades, differing in slopes from 5 to 20 degrees. The majority of these paths are provided with sign-boards giving distances and elevations.

A. W. Perry¹ has well said that there are cases in which an excessive amount of water (serum) in the tissues is practically the sole cause of the corpulency. He recommends Ranke's normal diet; namely, meat, 280 gm.; fat, 100 gm.; bread, 400 gm.; and the limitation of the amount of fluid ingested, allowing only 300 or 400 cc. more of water to be taken daily in drink and food than the daily amount of urine secreted. In order to carry out this method the percentages of water in different forms of food prepared ready to be eaten must be carefully estimated. These are "(numbers indicate percentages of water): Soup, 91.6; boiled meat, 70; roast mutton, 74; roast beef, 59; roast veal, 78; dried meat, 40; fish, white, 74; pudding, 48; mushes, 80; bread, hard, 30; bread, soft, 40; carrots, boiled, 82; spinach, 83; peas, 69.5; lettuce, 97; fresh fruits, 85; string beans, 88; celery, 84; asparagus, 94; milk, 87; cream, 65; cheese, 35; baker's toast, 1.18; crackers, 7.50; potatoes, boiled, 70."

Labbe and Furet² recommend a regimen from which salt is entirely eliminated, in connection with the ingestion of fluids in abundance, von Noorden gives an occasional "hunger-day."

Under any system of dietetic treatment the patient should be weighed accurately at brief intervals. The food should also be weighed and measured at first, but the patient soon learns to estimate by bulk the requisite quantity of each article permitted. The effect of treatment upon the general health must be noted. Fat-reduction must always be slowly progressive. If the case is one of plethoric obesity, a judicious rearrangement of the food, *e. g.*, a moderate increase of the protein substances and a corresponding diminution of the carbohydrates, is indicated. Muscular exercise, so far as possible in the open air, must also be enjoined—walking, horseback-riding, bicycling, rowing, swimming. The majority belong to this type, and the writer is in the habit of ordering the following dietary, with modifications to suit individual cases:

Morning Meal.—Fruit—as an orange, or one-half a grape fruit (without sugar), or a sour apple, wheat bread, $1\frac{1}{4}$ ounces (gm. 40); a soft-boiled egg; milk, 1 ounce (28 cc.); coffee, $4\frac{1}{4}$ ounces (120 cc.).

Noon Meal or Luncheon.—Caviare, 2 drams (gm. 8); lamb chops, boiled ham (cold), or fowl or game in season, 2 to 3 ounces (gms. 60 to 90); salad, 1 ounce (gm. 30) (with a small amount of French dressing); cheese, 1 dram (gm. 4); bread, rye, or bran, $\frac{1}{2}$ ounce (gm. 15); fruit (except strawberries and bananas), or (instead of the latter), water, 4 ounces (125 cc.).

Evening Meal or Dinner.—Soup (clear), 3 ounces (85 cc.); fish, 2 ounces (gm. 60); roast or broiled beef, lamb, veal, or game or poultry, 3 to 4 ounces (gm. 94 to

¹ *California State Journal of Medicine*, November, 1903, p. 358.

² *Revue de Médecine*, 1905, No. 9, p. 674

112.5); one or two of the following green vegetables: spinach, string beans, green peas, celery (stewed), asparagus, raw sliced tomatoes, Brussels sprouts, $1\frac{1}{2}$ ounces (gm. 42). For *dessert*, may take plain rice pudding, junket, cup custards (all sweetened with saccharin) or fruit (except strawberries and bananas) either raw or cooked, 4 to 5 ounces (gm. 125 to 150). May take 4 to 5 ounces (125 to 140 cc.) of water when fruit is not used.

No fluid is to be taken at meals except as indicated above, but a glass of water on rising, and three hours after food, is permitted. During the warm season, particularly if the sweat glands are active, an additional glass of water may be occasionally allowed.

In cases of anemic or hydremic obesity, the restriction of fluids may be more rigidly enforced. The rule, in such instances, is to favor concentration of the blood by not allowing more than 32 ounces of fluid *per diem*. In any given instance in which increasing weakness of the heart, with an impeded circulation, naturally diminishes the excretion of water by the cutaneous and renal routes, the consumption of fluid must be limited. In this form of the affection (anemic) the appetite is often impaired, and the dietary suited to the needs of the patients is exceedingly difficult to enforce.

The value of highly nutritious blood-making food—tender meats, milk, eggs, green vegetables, fruits—in this form of obesity is undoubted, and indicated first of all. The great difficulty in these cases is to accomplish the decomposition of proteins by muscular exercise, such subjects being lethargic and strongly averse to physical exertion. Fatty food which does not inhibit the disposal of the nitrogenous materials to the same extent as the carbohydrates should be considerably restricted. The superior value of this method has received adequate verification from personal experience. A light acid wine, as dry Moselle, Rhine, or claret, in definite quantity—4 ounces (120 cc.)—at dinner, is useful. The writer agrees with Osler that “in the treatment of extreme obesity the patient should be in a hospital or under the care of a nurse, who will undertake the proper weighing and administration of the food.”

The Mechanical Treatment.—To increase oxidation by exercise is, next to an appropriate dietary, the most important element. The special form of exercise, and also the duration and frequency, must be carefully adjudged for the individual patient. One of the principal uses of exercise is to maintain an appropriate proportion of albumin in the body, but “not only the fat but organic albumin is likewise used up by muscular activity” (Oertel). Physical exercise promotes the destruction of the fat already warehoused in the system, and, moreover, it invigorates cardiac action and induces deeper breathing. Muscular exercise, however, should not be too violent, particularly in patients manifesting circulatory disturbances. The writer’s best results have been from walking out of doors, later by increasing the pace, and, finally, climbing exercises either at home or at open-air health resorts, combined with gymnastics for the arms and trunk. The amount of exercise should be measured by the use of a good pedometer.

It is all-important to make the minutest study of the patient’s cardiovascular system, and to observe the effect of the muscular exercise. For example, if the case be one of the anemic, or hydremic type, then the patient must begin with short walks on the level, to be slowly and

gradually increased as the force of the heart and strength of the patient permit; and it is desirable to distribute the exercise over both the morning and afternoon hours if this is practicable. On the other hand, in instances of the plethoric form, a greater amount of physical exercise and even walks up inclines of moderate degree may be taken from the commencement. The so-called "resistance exercises," introduced by the Schotts in the treatment of chronic cardiac diseases, may be employed in the anemic or hydremic varieties in which cardiac dilatation is associated. Great care must be exercised in prescribing the mechanical treatment in obese patients who have atheromatous vessels. Complications must be relieved by appropriate treatment. When oxidation cannot be sufficiently promoted by muscular exercise, a course of rather deep massage, with Swedish movements, with a view to increasing the muscular system and stimulating the circulatory and eliminative organs, is the best substitute.

Although to a lesser extent than the muscular exercise, balneotherapy also promotes oxidation. When no contra-indications exist, cold- or salt-water baths followed by active hand-rubbing by the patient may be advised. These baths should be brief and the temperature of the water not too low at the start. If gouty manifestations are prominent, hot baths are to be employed preferably, since they increase elimination through the skin.

The treatment of associated diseases, many of which stand in the relation of cause is highly important—more especially gout. It is decidedly inadvisable to institute the usual reduction treatment when gout and obesity are combined, and such a course aggravates the first-named disease. The most brilliant results in such cases are obtained by adapting the treatment principally to the gouty element, although some of the measures employed favorably influence the obesity, *e. g.*, the physical exercise. On the other hand, there are numerous conditions and diseases associated with obesity in which the reduction treatment is called for and should precede.

Medicinal Treatment.—A number of watering-places, particularly Marienbad and Carlsbad, enjoy an enviable reputation for the treatment of obesity. From a therapeutic standpoint, however, a suitable dietary, muscular exercise, and other details, are equally important with the waters ingested. The spas are adapted especially to the plethoric form of the complaint, but not to the anemic. In the latter form, mild aperient waters, containing iron, are often serviceable. Neither should patients presenting marked cardiovascular disturbances resort to these spas. Such a course of treatment is not to be pursued except under the strict supervision of a resident practitioner. The results obtained are rarely permanent. In mild grades of plethoric obesity, such places as Hamburg, Kissingen, Brides-les-Bains, and Vichy, abroad, and Saratoga and Virginia Hot Springs, at home, may be recommended.

On the whole, the medicinal treatment is neither satisfactory nor successful. Certain remedies recommended are harmful—*e. g.*, *phytolacca* berry. Thyroid-feeding has come into more or less favor. Leichtenstein, Wendelstadt, Ewald, and others, have reported successful results

in a number of instances, especially in those exhibiting the anemic, flabby, "myxœdematoid" form of obesity. In a number of cases belonging to this category the use of thyroid extract (desiccated) in small doses caused a progressive loss of weight without injury to the general health; but it quite as often fails. In the majority the loss is not maintained after a reduction of 10 to 15 pounds. The commencing dose should be small and then slowly and gradually increased, but it is not advisable to exceed 5 grains (0.324) thrice daily. It is wise to guard the heart by combining small doses of strychnine or digitalis. Pituitary extracts have their advocates, but the writer has had no experience of their use.

In this connection it should be pointed out that a myxœdematous condition is not uncommonly associated with the anemic form of obesity.¹ Thyroidin, the active principle of the thyroid gland, and iodothylin, give results that are in every way comparable to those of thyroid-feeding. Symptoms of thyroidism—restlessness and tachycardia in particular—are the signal either for a reduction in the dosage of thyroid extract or its temporary withdrawal.

The cathartic mineral waters are indicated in cases in which there has been gormandizing with disturbance of the portal system, and in cases of plethoric obesity. When saline laxatives are employed the other fluids must be correspondingly reduced. The heart and bloodvessels must always receive the minutest attention.

Treatment of Local Obesity.—The best method is a course of local massage combined with a mild general-reduction cure. Allard² recommends the employment of a vibrating ball controlled by an electric motor in circumscribed obesity; this method of treatment has proved efficient in a limited number of cases. When the abdomen is the seat of the localized overfatness it is well to estimate the elements of intestinal distension, and gastrectasis when present and to institute appropriate measures, such as massage.

¹ "Some Respiratory Conditions Dependent upon Gout and Obesity," by the writer, *Philadelphia Medical Journal*, October 26, 1901.

² *Revue de thérapeutique*, 1905, No. 6, p. 191.

CHAPTER XX

RICKETS

By GEORGE F. STILL, M.A., M.D. (CANTAB.), F.R.C.P.

Up to recent times, certain conditions were included under the name of rickets which are now believed to be entirely distinct pathologically. The disease which is now called infantile scurvy (Barlow's disease) was formerly described as acute rickets, hemorrhagic rickets, or scurvy rickets; and under the head of fetal rickets was classed the disease which is now known as achondroplasia. Rickets will be described here under three heads: (1) congenital or fetal rickets, (2) ordinary rickets as seen in the first two or three years of life, and (3) late rickets. Congenital and late rickets are (in the opinion of most observers) extremely rare; moreover, there is still some doubt whether the conditions described by these names are in all cases identical pathologically with the common rickets of infancy. It will be convenient, therefore, to describe the common form of rickets first, for it is in this form that the characteristics of the disease have been most carefully observed.

Geographical Distribution.—There is a general consensus of opinion that rickets is more prevalent in temperate zones than in very hot or very cold countries, but this vague generalization rests on no firm basis. Rickets has a wide distribution in the northern hemisphere and, although figures are lacking for the southern hemisphere, the disease is known to be prevalent in Australia, South Africa, and South America. It is generally held that rickets is a disease chiefly of cities and large towns and probably the social conditions of town life are of much more importance in the etiology than any geographical limits.

Season.—Season plays little if any part, but several observers have noticed a special frequency of rickets among hospital patients during the winter months. This has been attributed to confinement in ill-ventilated rooms, but it is not proved that rickets has its *onset* more at one time of the year than another and there is an obvious reason why rachitic children should be brought for treatment during the winter months—a large proportion of the rickety children are not brought for rickets, but for respiratory complications and these are much commoner in the cold season than in the warm.

Age and Sex.—The onset is so insidious that any exact determination of the age at which it begins is usually impossible. It rarely begins after the age of three years, and probably seldom before the age of three months: among hospital out-patients the second year of life shows the largest proportion. Out of 1662 cases of rickets, 1268 were between one and two years old (Comby). Some statistics of consecutive patients

under the age of three years taken from the writer's out-patient clinic illustrate the relative frequency at various ages:

	Birth to 3 months.	Months 3-6.	Months 6-12.	Years 1-2.	Years 2-3.
Rickets	10	10	24	38	18
No rickets	31	24	22	27	20

It seems probable that there is little, if any, relation to sex. Out of 179 female children in the hospital, 73, that is 40.8 per cent., showed rickets, and 57 of 138 boys, that is 41.3 per cent.

Etiology.—Many different views have been held as to the etiology and no doubt several factors may play some part. But it may be said at once that, although there may be several predisposing or contributing causes, the one determining cause is faulty feeding or faulty assimilation. Rickets is, in fact, a food disorder. Recognizing this, however, we may well pay attention to those other factors to which more or less weight has been attached by various observers, for some of these may prove to be of importance in prophylaxis.

Overcrowding: Defective Hygiene.—Rickets is more frequent in cities than in country districts and this has suggested that defective hygiene is responsible for the disease. In many of the cities where rickets is most prevalent there is much overcrowding, and where a whole family of several children with their parents live in one room, the vitiated atmosphere may well interfere with the nutrition of an infant who spends the greater part of the day and night in this one room. Undoubtedly in London rickets is far commoner among the poorer classes than among the wealthy; but it seems likely that the difference lies much less in environment than in feeding. The children of the well-to-do become rickety when fed in the same way as the children of the poor. The minor part played by environment seems to be shown also by the fact that, in London at any rate, rickets is usually treated among hospital patients by simple dietetic measures and the administration of cod-liver oil, with no change of environment; and yet the results of such treatment are excellent. The same objections might be urged against the view that deficiency of sunlight is a large factor in the causation. In cities, with narrow streets and high buildings, the rooms of the poor are often ill-lighted and get little or no sunshine. But it is equally true that in some less-civilized parts of the world, where rickets is said to be extremely rare, it is customary to live in dwellings even less open to sunlight.

If, however, there is little evidence that overcrowding and squalor have much influence *per se* in the production of rickets, clinical experience seems to indicate strongly that certain conditions of city and town life do play a very important part. The struggle for existence in these crowded districts often makes it necessary that both parents should go out to work, and infants are therefore artificially fed; moreover, wherever poverty abounds, the cheaper substitutes for cow's milk are likely to be used, especially condensed milk. It seems probable also that, particularly among town-bred women, there is an increasing inability to suckle their offspring, which favors the occurrence of rickets.

Parental Influence.—Direct heredity has been held accountable by some (Hench, Pfeiffer, Ritter von Rittershain). Ritter found traces of rickets in the mothers of 27 out of 71 rickety children. But in the districts from which observations on this point have come, rickets is a common disease, and it is at least possible that parent and child have both been subjected in early life to faulty methods of feeding. The health of the mother during pregnancy has long been considered to have some influence upon the development of rickets in post-natal life. Phthisis during pregnancy is especially mentioned by Garrod and Fletcher¹ as a cause of rickets in the offspring, and the same writers consider that want of fresh air and exercise during pregnancy has a similar result; they mention, also, multiple pregnancy, and pregnancy at an advanced age, or at an unduly early age, as factors.

It is commonly stated that the last children born in a large family are more often affected with rickets than the earlier children, especially if the pregnancies have been not only numerous but in rapid succession. In such cases it is supposed that exhaustion of the mother interferes with the nutrition of the infant in some way so that some months after birth rickets appears. Similar in its effect, presumably, is lactation during pregnancy, which some observers have thought to be a cause of rickets in the offspring.

Whether any of these influences can be regarded as more than predisposing, is doubtful. Rickets at birth is generally thought to be exceedingly rare, and when the disease makes its appearance some months after birth, there is always a possibility and often a probability that post-natal factors, particularly the feeding, played a larger part in producing the disease than any parental influence before birth.

Syphilis.—Parrot's view that syphilis causes rickets is now generally discredited; but some still hold that syphilis strongly predisposes to rickets. Undoubtedly, some of the most severe degrees of rickets are seen when this disease is associated with congenital syphilis, and it would seem that in such cases the osseous and perhaps the visceral lesions of rickets may be modified not only in degree but also in kind. In the skull, osteophytic change is more common and more marked when syphilis is associated, although it may occur with rickets alone. Some have thought also that localized thinning of the cranial bones, craniotabes, is especially frequent when these two diseases are combined.

Dietetic Causes.—There are strong grounds for believing that dietetic influences stand in a much more direct relation than any of the foregoing. Put briefly, the facts are these: Rickets is uncommon, and in its severer degrees is exceedingly rare in infants who are having the breast milk only. It occurs almost invariably when the feeding has been such that the food constituents depart widely from the standard of human milk or include excess of carbohydrate whether in the form of sugar or starch. Rickets occurs in some of the lower animals, and in these it has been shown to be preventable by simple dietetic measures. Several observers claim to have produced changes resembling rickets

¹ *British Medical Journal*, September 21, 1895.

in animals by special methods of feeding. Rickets in children is successfully treated by suitable feeding without other measures.

As to the particular fault in the diet, some indication is obtained by a comparison of the methods of feeding in a series of rachitic children. These can be grouped thus in approximate order of frequency: (1) Starchy food; corn flour; potato; bread with more or less milk, fresh or condensed. (2) Condensed milk alone, often excessively diluted. (3) Proprietary foods, whether containing starch or not, and made with or without the addition of fresh milk. (4) Cow's milk diluted, without addition of cream. (5) Breast milk, with addition of starchy foods. (6) Breast milk only.

Great importance has been attached to the early use or to excess of carbohydrate food, especially starch. It is clear, however, from the occurrence of rickets in groups 2, 4 and 6, that the use of starchy food is not essential. There is some evidence that excess of sugar is not an essential factor, for in group 2, personal observations showed that rickets most often arose when excessive dilution of the condensed milk had been used so that the proportion of sugar was actually slightly below that in human milk; and in group 6 it is very improbable that any notable and prolonged excess of sugar should occur; for the average proportion of sugar in human milk is remarkably constant.

From the occurrence of rickets on a diet of condensed milk in watery dilution, it may be conjectured that the fault is one of defect rather than of excess, for all the constituents of milk in such feeding are usually present in unduly low proportion; moreover, compared with human milk this dilution of condensed milk will show a relatively greater defect of fat than of protein, as can be seen from the following comparison:

	Human milk.	Condensed milk as often given (about 1 in 10).
Protein	2.0	1.0 per cent.
Fat	3.5	.9 "
Sugar	7.0	5.4 "
Salts2	.2 "
Water	87.3	92.5 "

Analyses of human milk make it probable that deficiency of fat is commoner than deficiency of protein. When rickets occurs in an infant who has been fed only on cow's milk diluted, there has almost always been dilution sufficient to reduce the fat to half or less than half the proportion present in human milk, and this low proportion has been continued usually for many months. Such dilution reduces the protein little if at all below that found in human milk. When the proprietary foods are used, whether with fresh milk or without, analysis shows that there is almost invariably a deficient proportion of fat in the diet. All these facts suggest that deficiency of fat in the food is an important factor.

Failure of assimilation of fat may be as effectual as deficiency of fat-supply in causing fat-starvation. Any cause which weakens the digestive power, be it debility, disease, or the addition of indigestible food

to a diet which is correct enough in proportion of fat, may prevent absorption of fat and so produce rickets. Strong support has been given to this view by the observations of Bland Sutton upon animals in the Zoölogical Gardens in London. Young monkeys, bears, and lions died of rickets when fed on diets rich in protein but deficient in fat; the addition of fat to the dietary prevented the rickets. The value of cod-liver oil is in itself suggestive of the role of fat-starvation and from recent experience it would seem that any fat, animal or vegetable, provided it is easily digested, is equally curative of rickets. It is noteworthy also that those who have advocated the use of phosphorus have almost always used it in an oily solution.

While, therefore, it seems possible that deficiency of protein, and perhaps deficiency of certain salts, in the food may contribute in some degree to the production of rickets, there is strong evidence that the chief, perhaps the only constant, fault is deficiency of fat assimilation, whether this be due to a low proportion of fat in the diet, or to faulty methods of feeding interfering with digestion and so with the absorption of fat. It must be added, however, that some experiments on pigs, by Herter, of New York, showed that prolonged fat-starvation, although it produced muscular weakness and drowsiness, did not produce the bone changes of rickets (Freeman).

Pathology. — Morbid Anatomy. — The most obvious change is the enlargement at the junction of epiphysis and diaphysis in the ribs and in the long bones. This is due to changes in the two transverse zones at the junction of the epiphysis and diaphysis in a growing bone, the so-called "zone of proliferation" and the "zone of calcification." The bluish-gray zone of proliferation is enlarged so that it may be more than twice the normal thickness, and instead of being an even band with sharply defined edges limiting it from the cartilage on the one side and the zone of calcification on the other, it is quite irregular, especially toward the zone of calcification, where, even with the naked eye, it can be seen that the two zones are mixed together, islets of calcification are seen amidst translucent cartilage, and irregular processes of cartilage extending into the region of calcification, and the whole is abnormally vascular, so that to the naked eye, numerous vessels are obvious, traversing these confused zones in all directions.

Histologically, there is the same confusion; the cartilage cells are more numerous than they should be, the arrangement of columns has lost its regularity; they are ill-formed and no longer parallel. Between them in many places are areas of calcification, sometimes even of fully formed laminated bone, lying amid cartilage cells and cartilaginous matrix in which are numerous vessels passing inward from the adjacent periosteum or perichondrium. The cancellous tissue of the shaft has also an undue vascularity, and the absorption of this tissue which should proceed but slowly, keeping pace with the formation of new bone from the periosteum without, proceeds in rickets too rapidly, so that the bone consisting of an imperfectly ossified layer without, is further weakened by the rarefaction and looseness of its cancellous tissue within.

The subperiosteal formation of bone is also disturbed, the periosteum

itself becomes thickened and the proliferating layer beneath, in which calcification should occur, is excessively vascular, and contains abundant cell elements, but is imperfectly calcified, and the production of true laminated bone is deficient, so that the bone here also is softer than normal and bending easily occurs. The bone thus formed may be of spongy character, a condition especially noticeable in the thickened areas of the parietal and frontal bones, where also the vascularity is sometimes so great that it can be observed clinically as a bluish discoloration seen through the tense scalp.

Muscles.—It is stated that the muscles show microscopically some blurring of striation, and that there is excess of fat in the connective tissue between the muscle fibres. In severe cases, fatty degeneration of the muscle fibres themselves has been observed.

Viscera.—The liver is sometimes enlarged, and the spleen also to a slight degree. In both some observers have found slight increase of fibrous stroma, but the relation of this to the rickets is uncertain. The lungs show no characteristic change.

Pathogeny.—**Chemistry of Rickets.**—The chemical pathology is at present entirely unknown. Of the several theories, none rests upon a satisfactory basis; experiments and observations have been discordant and contradictory. The facts which have to be explained are not merely the softening and bending of bone, but the overgrowth of cartilage, the perversion of the whole process of bone formation, and in addition more general disturbance, especially in the nervous system, and also in the muscles and viscera. There is evidently some wide disturbance of metabolism. One of the few points upon which there is agreement is deficiency of lime salts in the bones. Deficiency of lime in the food was found by Chossat (1842) to produce fragility of bones in pigeons, and recently Stoeltzner, by feeding puppies on lime-deficient food, produced softening of bones; but mere softening or fragility of bones is not rickets, and it has been shown both by Friedleben and by Stoeltzner that the changes produced in these experiments are not those characteristic of rickets.

Deficient absorption of lime salts has also been suggested, but if this were so the lime salts eliminated in the urine might be expected to be increased; some observers have found this to be the case, others have found no difference. Cow's milk contains 0.15 per cent. of lime, whereas human milk contains only 0.02 per cent. of lime (Cautley); it is evident, therefore, that even when cow's milk is given greatly diluted, much more lime is supplied to the child than when breast milk is used: but rickets is very much commoner in children fed on cow's milk than in those fed only on breast milk. The facts that lime-water has no therapeutic value in rickets, and that rickets is so common in districts where the water contains much lime, are also noteworthy, but it is possible that for the absorption of lime, its administration in organic combination may be important.

A relative deficiency of lime, rather than an absolute, has been suggested by Kassowitz, who assumes that some irritant, possibly absorbed from the gastro-intestinal tract, causes chronic hyperemia, with result-

ing overgrowth of bone tissue, but no corresponding increase of lime salts, and thus leads to imperfect calcification. Solution of lime salts by lactic acid or carbonic acid in the blood has also been suggested, but there is strong evidence, clinical and experimental, against this view. Nor is there any satisfactory proof that excess or deficiency of phosphates in the food is a cause of rickets.

Some experiments recently made by Freund seem to show that fat in the diet promotes the absorption of phosphates. This observation would connect fat deficiency in the diet and the therapeutic value of fats with the deficiency of calcium phosphate in rickety bones.

The problem is obviously extremely complex and no mere chemical formula is likely to explain a condition which is intimately bound up with biological processes of which at present we know but little.

Bacteriology.—Experiments with injection of various microorganisms and with pieces of bone and feces from rachitic infants have failed to produce the disease. There is at present no proof that rickets is ever caused by bacterial infection.

Symptoms.—Rickets is a disorder of nutrition, and, as such, affects the whole organism. The bone changes are only part of a general disease. Much of the confusion as to the pathogeny and even the diagnosis has resulted from the tendency to concentrate attention upon the osseous lesions to the exclusion of other features. A child may suffer severely and yet show so slight a degree of rachitic change in the bones that the disease might almost pass unnoticed if only the osseous system were considered. The stress may fall upon the nervous system in one case, upon the muscular in another, and perhaps even upon the blood and blood-forming tissues in a third.

Before describing the symptoms in detail, an outline of a typical and well-marked case of rickets may be given. An infant aged about eighteen months is brought for inability to walk. He has been suckled entirely perhaps for six or seven months, and then has had condensed milk and occasionally bread or potato. For some months past, he has sweated profusely about the head and neck whenever he falls asleep. Dentition did not begin until he was nearly a year old, and even now he has but three or four teeth. He has never walked, and sitting on the mother's lap there is a marked kyphosis especially in the upper lumbar region. He is pale and fretful; perhaps rather fat, but flabby; the head is unduly large, with a tendency to squareness; the anterior fontanelle is much more widely open than it should be at this age. The chest is ill shaped, the sternum a little prominent, and there is some transverse constriction below the level of the nipples. A row of knob-like eminences mark the junctions of the costal cartilages with the ribs on each side of the chest; the lower ribs are somewhat everted above the big abdomen, in which the liver can easily be felt, and the spleen is also just palpable. The muscles feel flabby and soft. Just above the ankle and the wrist, the bones seem thickened. There is little or no abnormal curvature of the bones.

Such is a moderate degree of rickets; but there are many more in which the symptoms are altogether less marked, and perhaps delay of

dentition and of closure of the fontanelle, with slight thickening at the costochondral junctions (beading of the ribs), and possibly, but not necessarily, some enlargement of the radial epiphyses, are the only evidences of the disease. There are also cases, much less frequent, in which the symptoms are altogether more severe, the limbs are deformed by bendings and distortions of the bones, the cranium is irregularly thickened or thinned, and the child perhaps shows severe nervous symptoms, convulsions, or laryngismus stridulus.

Nutrition.—The child is often unduly fat, especially in slight, or moderate degrees of rickets. This deposit of fat is apparently derived from carbohydrate food, for it is seen when the diet is greatly deficient in fat. It would seem that this stored fat is unable to replace the functions of fat taken as such in the food. In severe rickets wasting of greater or less degree is common.

Head Sweating.—This is often one of the earliest symptoms and may be so profuse that the pillow is soaked. It usually occurs when the child falls asleep; it is not present in all cases. Probably with this is associated a feeling of heat, for the infant at this stage is very apt to push the bed-clothes off at night and lie uncovered.

Temperature.—This is normal in most cases even during the most active stage, so far as the writer's observations go; a rise of temperature is almost always due to some complication.

Teeth.—Delayed dentition is one of the most constant symptoms. In 32 out of 42 consecutive cases, between nine months and three years old, this was present. Frequently no teeth have appeared at the end of the first year. Rarely their appearance is delayed beyond the age eighteen months. There is a striking tendency to very early caries; even before the tooth is fully cut the enamel at the cutting edge is often completely destroyed. If dentition has begun before the onset, it is often arrested for several months.

Muscular Weakness: Laxity of Ligaments.—Muscular weakness is a very common result in the active stage, and in the more severe cases is almost always well marked. It may be quite out of proportion to the osseous changes, and for this reason is liable to be mistaken for some paralysis of nervous origin; it may be so great that a child of two or three years is unable to stand or even to sit up. The late acquirement of sitting, standing, and walking, is chiefly due to this weakness, though in part, no doubt, to laxity of ligaments, and to bone changes. The child who has already begun to stand often loses this power at the onset. The stooping of the back, or kyphosis, which is common in rachitic children, would seem to depend chiefly upon weakness of the muscles of the back. It is possible that muscular weakness of the respiratory muscles plays some part in the tendency to pulmonary affections.

The effects of muscular weakness are intensified by laxity of the ligaments, apparently as the result of some structural change which renders them soft and yielding. The child can often place his toes behind the ears without difficulty; and the head of the tibia shows an undue amount of lateral mobility, so that it can be loosely knocked against the condyles of the femur. Both these changes, the muscular and the

ligamentous, contribute to some of the deformities, such as talipes valgus and planus, genu valgum and varum, and lateral curvature of the spine.

Osseous Symptoms.—These are the outcome of the delayed and imperfect ossification, hyperplasia, and abnormal absorption of bone tissue. The most frequent manifestation is the so-called “rickety rosary,” or beading of the ribs, a thickening at the costochondral junction which in a thin child can be seen and in others easily felt. These beads are usually largest and most readily felt on the fifth, sixth, and seventh ribs, and in a mild case may be scarcely perceptible on other ribs. They are often seen postmortem to be more marked on the internal than on the external surface of the thorax. The internal bead, however, is sometimes exaggerated by a displacement of the bony rib backward at the costochondral junction, so that, instead of joining the cartilage end to end, it joins it at an angle which projects on the inner aspect of the thorax (Fig. 50). In such cases the external beading may be obscured altogether, and the junction of rib and cartilage forms a depression externally, so that, clinically, beading may not be detected. The rickety rosary is one of the earliest symptoms and is often the only bone change to be found during life. It gradually diminishes after the fourth and fifth year and has usually disappeared before puberty.

As a result of the backward displacement of the anterior portion of the rib, in some cases there is an exaggeration of the angle of the rib, posteriorly, or actually a green-stick fracture at that situation; the projections formed thus are sometimes described as “posterior beading,” but are obviously different in their pathology from the anterior “rickety rosary.”

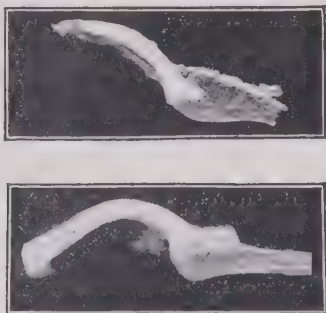
Enlargement of epiphyses is a very common symptom. It is generally most marked at the lower end of the radius, where some thickening was present in 64 per cent. of the writer's cases. At the lower end of the femur and tibia it is also frequent. Other long bones show it less frequently. The ends of the phalanges of the fingers are occasionally affected, giving a somewhat spindle-shaped appearance. Some thickening of the diaphysis of the phalanges has also been described (Koplik).

Owing to the softness of the bones, some degree of curvature in the limbs is common: 43 per cent. of the writer's patients showed curvature of the bones either in the upper or in the lower limbs, but in most of these the bending was slight in degree. The commonest deformity of this kind is a bending outward of the lower third of the tibia—sometimes there is combined with this, or alone, a forward bend which may be slight or may be sharply angular in the lower third (Fig. 51).

The femur is less often affected; it shows a general outward curve in children who are already able to stand or walk when the rickets affects them. In children who are carried about on the nurse's arm, the curve in the femur is often anteroposterior with the convexity forward. A much rarer result is the condition known as “*coxa vara*,” in which the head of the femur is bent downward so that it is at the same level with, or even lower than, the great trochanter, while the neck of the femur is curved with the convexity forward and upward. Bending of the bones of the upper limbs takes place chiefly in children who spend much of their time crawling about or in the sitting position supporting the

weight of the trunk partly upon the hands; a favorite position is that shown in the illustration (Fig. 52), where the child sits tailor-wise and uses its hands as a prop. Both the humerus and the bones of the forearm are usually curved outward in such cases. The clavicle, in severe cases, often shows a sharp angular bend forward and upward at the junction of the inner and middle third; and sometimes there is evident

FIG. 50

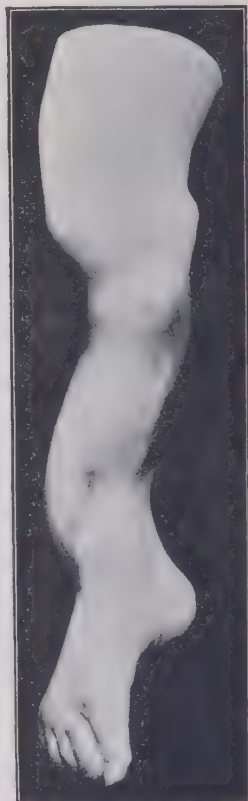


Anteroposterior section of costochondral junction to show rachitic displacement. In the upper specimen the displacement is slight, in the lower there is complete displacement.

thickening here, the result of a green-stick fracture. All these deformities are the result partly of pressure from without, partly of the weight of the body, and partly of muscular traction upon the softened bones.

Similar in their production are the rachitic deformities of the thorax and pelvis. The former shows a lateral contraction so that the sternum and costal cartilage appear to project forward in front of the ribs, while the depression at the junction of each rib and cartilage forms a furrow passing downward and outward and usually lost in a deeper transverse groove just below the level of the nipple, the so-called "Harrison's sulcus." This sulcus, which extends from the ensiform cartilage to the posterior axillary line, is commonly associated with eversion of the lower ribs over a distended abdomen which increases the distorted appearance of the chest. The pigeon chest (*pectus carinatum*), in which the ribs appear straightened as they pass from the posterior axilla to join the prominent sternum so that the cross-section of the thorax would be roughly triangular with the apex at the sternum, is often described among rachitic deformities. Neither pigeon chest nor "Harrison's sulcus" are essentially rachitic. They are seen in any condition in which there is obstructed respiration.

FIG. 51



Photograph of a cast at the museum of the Hospital for Sick Children, Great Ormond Street, London, showing a common rachitic curvature of tibia.

Pelvic deformities hardly enter into the clinical picture of rickets in childhood, for they attract no attention at that age, although in the adult female they become of great importance. Rickets here, as in the rest of the bones, may arrest development, so that the pelvis remains small and generally contracted. Often there is in addition flattening of the pelvis anteroposteriorly; it is shallow, and, occasionally, from traction of the muscles and the pressure transmitted from the spine and from the femora, more marked distortion takes place.

FIG. 52



Common position of rickety child with bending of forearm, showing also large head, large abdomen, and deformed thorax with Harrison's sulcus.

The bones in rickets become not only soft but brittle, so that fractures, usually of green-stick character, are apt to occur in severe cases with little evidence of traumatism, sometimes apparently from muscular traction alone. This tendency depends partly on absorption of cancellous tissue in the rickety bone, partly on deficient calcification, and partly perhaps upon some abnormal arrangement of the trabeculae.

As a result of the epiphyseal affection and of the sclerosis which may occur in the bones after the rachitic process has ceased to be active, permanent stunting of growth occasionally takes place, so that the child may be undergrown or actually dwarfed for the rest of its life.

Cranium.—One of the most constant symptoms is delay in the closure of the anterior fontanelle. Normally this should measure about $\frac{3}{4}$ to 1 inch (2 to 2.5 cm.) anteroposteriorly and transversely at the end of the

first year and should close at or about the age of eighteen months. In rickets, it often measures 2 inches (5 cm.) in both directions at twelve months, and is frequently open as late as two and a half or three years; the writer found it open at four and one-half years. This delay of closure is not due to any general expansion of the skull such as occurs in hydrocephalus, for it occurs equally where there is no enlargement of the head and where the head is, as often happens in rickets, unduly large; it indicates rather a general backwardness in bone formation which may determine more extensive failure of consolidation in the cranium so that the interparietal and the parietoöccipital sutures are not firmly united for many months.

The size of the head is commonly above the normal; in 17 cases of rickets with an average age of 4.72 years, Lucas¹ found that the average circumference was 21.2 inches (54 cm.), whereas in 17 non-rachitic children with an average age of 6.05 years, the average circumference was 19.95 inches (50.5 cm.). The cause of this increase in size is uncertain; sometimes the brain has been found above the average weight and in some cases there is considerable thickening of the bones of the skull, though hardly sufficient to account for the large size. The rachitic skull differs from the normal not only in size but also in shape. Two types may be recognized. In the one, the more frequent, the skull is flattened on the vertex and tending to squareness; the posterior segment especially is enlarged; in the other the head is narrow from side to side and elongated anteroposteriorly. The softening of the bones is shown in the skull by the deep grooves which are hollowed out on its surface by the veins of the scalp so that their course can easily be traced by running one's finger-nail along the groove.

The relation of bossing of the skull and of craniotabes to rickets has been much disputed. Both have been attributed to syphilis by some, and to rickets by others. So far as personal observations go, both seem to occur in rickets apart from syphilis but to be aggravated when syphilis is added to rickets. Some have thought that the symmetrical bosses which occur on the frontal and parietal bones, giving rise to the "*caput quadratum*" or "*hot-cross-bun head*," can be distinguished by their position from those of syphilis, which are said to be closer to the anterior fontanelle. However this may be, there are certainly two conditions, very different in appearance, which give rise to the local thickenings felt on the skull. In the one, the surface of the bone is smooth and the thickening is due to a very vascular increase of the cancellous tissue between the compact inner and outer tables; in the other, there is a deposit of vascular spongy bone on the outer surface of the skull, which has a roughened, worm-eaten appearance. Whether these represent different stages of one and the same process or whether they indicate different processes is at present uncertain.

The term "craniotabes" is used with varying significance. Some would apply it to a diffuse yielding of bone near the sutures, especially about the parietoöccipital sutures, which is not uncommon in rachitic

¹ *Pathological Society Transactions*, xxxii, 359.

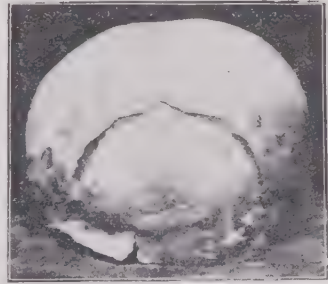
children under twelve months of age and is exceedingly common in infants during the first two months of life. In early infancy this thinness of the bone is often associated with unusual separation of sutures and patency of the fontanelles, posterior and lateral as well as anterior. It is very doubtful whether such a condition should be taken as necessarily indicating rickets; certainly it is quite common during the first three or four months of life in breast-fed infants, particularly those of small size and generally feeble development, with no other evidence whatever of rickets.

Much more significant are localized patches of thinning of the bone situated generally in the occipital or in the parietal bone (more commonly the latter) near to, but not actually adjoining, the parietöoccipital suture, from which they are separated by an area of firm bone (Fig. 53). The patches are usually about $\frac{1}{2}$ to 1 inch (1.5 to 2.5 cm.) in diameter, round or oval, and can be detected by taking the head between the palms of the hands so that the fingers rest on the posterior parietal and occipital region. On pressing firmly with the fingers, the affected areas are felt to yield, bulging inward like a piece of thick parchment and rebounding when pressure is removed. In severe cases these areas run together, but even then the irregular and patchy distribution distinguishes them usually from the diffuse thinness mentioned above. This condition, unlike the diffuse thinness of the edge of the bone, is often found when the sutures are well closed and only the anterior fontanelle remains patent. It occurs often in the second year of life in children who have only developed rickets after the skull bones are already well ossified. It is an absorption of already formed bone, not a mere delay of development as the diffuse thinness with patent sutures probably is in some cases.

According to the meaning attached to craniotabes, its frequency has varied in statistics. According to some recent observations made by S. Fraser upon children under three years of age at the Children's Hospital, Great Ormond street, London, 29 per cent. of the rickety children showed craniotabes, but this series included many cases in which there was only yielding of the bones near the sutures.

There can be no doubt that craniotabes occurs with rickets without syphilis. In the form of isolated patches it is associated particularly with laryngismus stridulus and tetany, the former of which, if not also the latter, when it occurs in childhood, occurs almost exclusively in the rachitic and has no connection with syphilis. Out of 21 cases of laryngismus stridulus in which the writer noted this point, craniotabes was present in 7. According to Barlow and Lees, 47 per cent. of cases of craniotabes show evidence of syphilis; but many of their cases with syphilis had rickets.

FIG. 53



Posterior view of rachitic skull, showing characteristic areas of true craniotabes.

Nervous Symptoms.—*Mental.*—The rickety infant is often fretful and peevish, but perhaps more from the discomfort of prolonged ill-feeding than from any direct effect of the disease. In later childhood, rickets has been described as a cause of precocity, and the large head has been supposed to allow a larger capacity for mental development. Thackeray has been quoted as an instance. The accuracy of these observations is very questionable; the child who is invalided by any chronic disease is likely to be much with its elders and to acquire a precocious manner. The writer is unable from his own observation to affirm any intellectual superiority in rachitic children. There is no evidence that they are inferior, although it was stated by Sir W. Jenner that "Children the subjects of extreme rickets are almost always deficient in intellectual capacity and power."

Convulsive conditions are the chief evidence of rickets affecting the nervous system: from about the sixth to the twenty-fourth month convulsions in infancy are most often due to it. The cortex is in some way rendered so unstable that trivial exciting causes, such as constipation or dentition, are sufficient to induce an attack. As part of this convulsive tendency must be reckoned laryngismus stridulus and tetany with their almost constant accompaniment—the so-called "facial irritability."

In *laryngismus stridulus*, a spasm of the larynx suddenly closes the glottis so that the infant is for a few seconds unable to draw air into the chest: the face becomes livid, the infant looks terrified, and makes violent efforts to inspire. After a few seconds the spasm relaxes and a deep inspiration is taken with a loud crowing noise. These attacks come on usually when the infant begins to cry or just as it wakes, or a sudden draught of cold air may start them. There may be many in the day, or only two or three in a week. If the spasm is prolonged many seconds, the infant becomes cyanosed and may pass into a general convulsion, or may die silently of asphyxia. These attacks occur most often between the ages of six and eighteen months; they are rare after the age of two years. Of 35 cases, 32 showed definite rickets, 2 probable rickets; only 1 showed no bone manifestations of rickets.

Tetany, a tonic spasm affecting chiefly the muscles of the forearm and hand, and leg and foot, is in young children almost always associated with rickets. The hand is generally slightly flexed at the wrist, the thumb is adducted so that its tip points to the interval between the ring and the mid-finger, the rest of the fingers are semiflexed at the metacarpophalangeal and extended at the phalangeal joints, often with some tendency to overextension at these latter. The toes are crowded together in a position so far as possible resembling that of the fingers; the foot is sometimes extended at the ankle. Apparently from some pressure on veins by the contracting muscles, œdema of the hands and feet is often seen with the tetany. The spasm of tetany is in some cases persistent for several hours or even for days; in others it is intermittent, lasting only a few minutes at a time and causing some cramp-like pain each time it recurs. It is most frequent at the age at which laryngismus stridulus is common, and is usually associated therewith.

A latent form of tetany is not uncommon in rickety children; it is

demonstrated by the method described by Trousseau: the upper arm is firmly grasped in such a way as to compress the vessels and nerves on the inner side of the arm, and after a period varying from thirty seconds to about two minutes, the hand assumes the characteristic position of tetany.

Of 24 cases of tetany in young children, 22 showed definite rickets, 1 doubtful rickets, and 1 no bone manifestations of rickets. Twenty-three of these cases were associated with laryngismus stridulus.

Facial irritability, Chvostek's sign, is also closely related to the convulsive manifestations of rickets. On gentle tapping over superficial branches of motor nerves, a contraction of the corresponding muscles occurs. This was first described with regard to the face, but is to be seen in the limbs also. Of 35 cases of laryngismus stridulus, 33 showed this nerve irritability; and it is almost always present with tetany whether this is associated with laryngismus stridulus or not. Facial irritability is found in rickets also apart from laryngismus stridulus and tetany, and is then probably always an indication of a convulsive tendency. In some of these cases there is a history of preceding convulsions; in others, after the facial irritability has been observed, convulsions occur. It is therefore of practical value as indicating the need for such drugs as bromides, by which convulsions may be averted. This nerve irritability is probably most common in the face, but as the writer has notes of cases in which it was in the limbs only, the term facial irritability is not sufficiently inclusive.

Head nodding with nystagmus (*spasmus nutans*) needs only to be mentioned here, for, although it is generally associated (Hadden, J. Thomson), the rickets is regarded only as a predisposing cause.

The pronounced nervous instability may show itself in other ways—a rhythmic head-rolling upon the pillow so that the back of the head is rubbed almost bald, or a head banging in which the child beats its head with its hands or against any object near, are both seen most often in rickety children, although the determining cause may be some peripheral irritation, dentition, or middle-ear catarrh.

Hydrocephalus was regarded by Jenner as sometimes produced by rickets but this view is now generally discarded. The large head of rickets, especially when the square shape is less pronounced than usual, may simulate hydrocephalus, but is probably rarely, if ever, due to distension of the ventricles.

The association of zonular or lamellar cataract with rickets, and especially with convulsions, has been noticed by several observers since Davidson and Horner of Zurich first drew attention to it in 1865.

Tenderness.—It is generally stated that there is some tenderness present not only in the bones but also in the muscles (Gee). Hilton Fagge described this as one of the characteristic features. If such a condition occurs at all, it must be quite exceptional. The rickety child is often fretful and nervous, resents, or is frightened by, any examination; but if there is definite tenderness, the presence of scurvy with the rickets should be suspected.

Gastro-intestinal Symptoms.—The abdomen is usually distended so that the rachitic "pot-belly" has become a recognized term. The distension is due to three causes: flatulence arising from improper feeding; displacement downward of the liver and spleen by eversion of the lower ribs; diminished space in the small pelvis; probably to these may be added relaxation of the abdominal muscles so that they afford less support than normal. As a result of this distension, the recti muscles are often separated so that there may be a gap of 1 inch (2.5 cm.) between them; but this is not peculiar to rickets; it occurs in young children with chronic distension of the abdomen from any cause. In the gastro-intestinal, as in the pulmonary mucosa, there is a special tendency to catarrh.

The liver is often to be felt 1 inch (2.5 cm.) or more below the costal margin, but this is due in many cases, partly at least, to displacement downward by eversion of the ribs. The spleen, for the same reason, is often felt $\frac{1}{2}$ to 1 inch (1.5 to 2.5 cm.) below the costal margin; it is probably but seldom enlarged to any considerable extent, unless the condition known as splenic anemia is to be regarded as a manifestation of rickets.

Respiratory System.—The laryngeal spasm has been described. Bronchitis is very frequent in rachitic children and this tendency is favored, in severe cases, by the softness of the ribs and the weakness of the respiratory muscles. There is, in fact, a vicious circle. For the mechanical reasons mentioned, the lung is very imperfectly filled with air and the collapse thus induced favors the occurrence of bronchitis and hence further collapse. The movements of the diaphragm also must be rendered less extensive by the eversion of the lower ribs, and at the same time hampered by the abdominal distension.

Circulatory Symptoms.—Anemia is common and sometimes very profound. In severe cases the child may have a waxy complexion not unlike that of chlorosis, and Hutchison has referred to cases in which the blood changes corresponded. In a rickety infant, aged one year and seven months, the blood showed four million red corpuscles and only 20 per cent. hemoglobin. The leukocyte count shows nothing characteristic; some observations by Thursfield and Drysdale¹ gave the following results: Hemoglobin, 44 per cent.; red corpuscles, 4,364,000; white corpuscles, 11,000; polymorphonuclears, 49.2 per cent.; lymphocytes, 46.8 per cent.; large mononuclears, 3.3 per cent.; eosinophiles, 0.5 per cent.; myelocytes, 0; occasional nucleated red corpuscles. This agrees very nearly with the average proportions of the differential count for a healthy infant of about twelve months, except perhaps for a very slight increase of polymorphonuclear cells.

A systolic bruit is frequently heard over the open anterior fontanelle, and was formerly thought to be of value in the diagnosis between a rachitic and a hydrocephalic head (Rilliet and Barthez). It is, however, as Osler² has shown, frequent in infants and young children who are free from rickets; it is heard most commonly in the second year of life but may be heard as late as the sixth year.

¹ *Med.-Chir. Society Transactions*, 1904.

² *Boston Medical and Surgical Journal*, No. 2, ciii, 20.

Complications.—Bronchitis is extremely frequent; bronchopneumonia is also common and is one of the chief sources of danger to life, especially where there is much rachitic deformity of the chest. Gastro-intestinal catarrh and diarrhoea are common accompaniments and considerable dilatation of the stomach is sometimes evident both clinically and post-mortem. Infantile scurvy is an occasional complication, but the association is to be regarded as a coincidence; there is no essential connection.

Diagnosis.—The clinical picture of severe rickets is so striking that it can hardly be mistaken. The projecting rickety rosary, the large epiphyses, the large square head, the bent limbs, are characteristic enough; but in slight cases the difficulty is greater and it is clear from a comparison of various observers' statistics that there is no general agreement as to what constitutes evidence of rickets. For instance, in Munich at the same institution one observer found about 70 per cent. of the children under two years to be rickety; another observer found that less than 5 per cent. of the children were rachitic.

Beading of the ribs has often been accepted as evidence of rickets, but this is not necessarily so; it is common to find beading of the ribs in healthy infants just after birth, and Escher found on microscopic examination that these showed none of the characteristic changes of rickets. Yielding of the skull bones on pressure, a diffuse thinness along the edge of the bones with some separation of sutures, has been taken as a proof of rickets, but this also is incorrect. A simple delay of development occurs quite apart from rickets and Fede and Finizzio concluded from a microscopic examination of the skull bones that the yielding of the skull in newborn infants was not necessarily due to rachitic change.

It seems probable that there are other bone diseases which may cause softening of bones or deficiency of calcification, so that bending or fracture of bones results. Osteomalacia, or *mollities ossium*, in which at an age usually beyond puberty the bones show progressive softening so that they bend in all directions, is probably quite distinct in its pathology as it usually is in its course. Occasionally cases are seen in childhood with extreme softening and bending of bones and lacking the usual characteristics of rickets, such as the enlarged epiphyses and the large square head. Some of these cases are probably much nearer allied to the so-called osteomalacia of adults. It may be that in some cases a condition like the osteoporosis produced experimentally in puppies occurs in children also.

The weakness of the limbs may be mistaken for infantile paralysis; the general distribution, the gradual onset, the retention of reflexes and the changes in the bones will usually suffice for the distinction.

The kyphosis may be so marked as to suggest spinal caries; it is generally taught that the curve of rickets disappears when the child is held up supported under the armpits, whereas that of spinal caries remains. In long-standing cases, however, the kyphosis may not disappear thus, nor even when the child is made to lie on its face, and the diagnosis has to be made from the more general curving of the spine and from the association of the kyphosis with marked rickets elsewhere.

The enlargement of the head is sometimes difficult to distinguish

from that due to hydrocephalus. As a rule the flattening of the vertex and the square shape distinguish the rachitic head from the more globular hydrocephalic head; but there are cases in which, if the child is first seen after the fontanelle and sutures have closed, the diagnosis may be impossible; and it is only when symptoms result from increasing tension in the ventricles that the question may be settled.

Course and Prognosis.—Rickets is readily amenable to treatment, and when once the disease has stopped, any recrudescence is very exceptional. Probably, some of the cases described as late rickets are of this nature. The intensity and duration of the symptoms vary chiefly according to the feeding; no doubt, in some cases as the child grows older and takes a more varied diet, which includes a sufficient proportion of the requisite constituents, the disease comes to a standstill without special treatment. In others it progresses so rapidly that within a few months considerable softening and bending of bones occurs, nervous and respiratory symptoms become pronounced, and the child dies. When death results from rickets, the immediate cause is usually bronchitis or bronchopneumonia, convulsions, or laryngismus stridulus.

Rickets is seldom seen in active progress after the age of three years, but the deformities produced may last for life. In their slighter degree however, some of these may disappear: the beading of the ribs is gradually lost in many cases and even considerable deformity of the chest may diminish greatly as the child becomes stronger and expands his lungs more thoroughly. Slight curvature of the legs may right itself if the child is kept off his feet for several months while suitable treatment is used.

Treatment.—Prophylaxis.—Rickets is in large measure a preventable disease, and as it is due chiefly to faults of diet so its prevention depends almost entirely upon dietetic measures. The surest safeguard is the continuance of breast-feeding alone for nine or ten months, and the use of fresh milk as the chief article of diet until the end of the second year. It is important to realize that breast-feeding does not protect from rickets when other food is given at the same time. An infant suckled, and at the same time receiving farinaceous food, often develops a marked degree of rickets. Even when an infant has been suckled entirely for the first nine or ten months, this does not prevent the onset subsequently if the feeding is then unsuitable. It is probable that the liability becomes gradually less after the end of the first year; in other words, of the large number of cases seen in the second year, most have had their onset at some period within the first twelve months; but there are certainly some in which the disease began in the second year. For this reason the diet in the second year requires care as well as in the first. A common fault is to allow the child much farinaceous food to the neglect of milk. Milk should certainly be the staple diet until the child is two years old.

There is no doubt that the early use of farinaceous food plays a large part, and it is the writer's belief that even the small proportion of starch present in barley-water has this tendency and should be avoided during the earlier half of the first year. Few infants are the better for any

starch addition to the diet before the age of nine months, and even then its introduction should be very gradual. It should be added first only to one meal daily, and when the infant is twelve months old should not be given in more than two meals. The rest should consist of milk to which raw meat juice may be added. The yolk of an egg, lightly boiled, may be allowed at this age. Potatoes are to be avoided altogether until the age of eighteen months, and even then only very little, thoroughly mashed with milk, should be allowed. During the second year the child should not take less than one and one-half pints of milk daily.

Where hand-feeding is inevitable, careful modification of fresh milk is necessary. It is not sufficient to order cow's milk diluted with water; the proportions must be properly adjusted. The fault in such cases is probably the deficiency of fat, and for this same reason rickets is a common result of many of the proprietary foods whether mixed with fresh milk or not and whether containing starch or not. It would seem that a proportion of fat under 2 per cent. for infants over the age of six months involves some risk, and that a proportion of fat under 1.5 per cent. given for several months at any period of infancy involves a high probability of rickets. The addition of cream to the diluted milk is an important preventive measure, and if circumstances make this impracticable, the milk should be given as little diluted as possible. Where deficiency of fat is combined with the too early use of starch or with excess of carbohydrate, as in many of the proprietary foods, the risk is greatly increased.

Other possible factors should also be considered: the child should be out in the open air three hours daily or more if possible, and the rooms in which he lives should be well ventilated and get plenty of sunlight.

If rickets has appeared, much may be done to prevent bending of the bones by such measures as avoid the pressure of the body or other weight upon the limbs. Standing, and walking especially, should be forbidden until the remedies, dietetic or otherwise, which are employed have had time to diminish the softness of the bones and the laxity of the ligaments and muscles. This may take several weeks. The greater vigor of the child's movements, the disappearance of sweating, and the increased activity of dentition, afford some indication of improvement; but in a general way with a marked degree of rickets, if the child has already begun to stand before the symptoms attract attention, he should be kept off his feet altogether for at least three months from the time when treatment is begun, and if standing has not yet been acquired the parents should be instructed not to encourage the child to attempt to stand.

In severe rickets in the active stage even sitting should be discouraged, for apart from the kyphosis and lateral curvature which are usually transitory, the occurrence of pelvic deformities is favored by the pressure from above and below incurred by the sitting position. In cases where much deformity of the chest has occurred, with sinking in of the ribs in the axillary region and prominence of the sternum and cartilages, the danger of bronchitis and bronchopneumonia is to be remembered, and every precaution taken to avoid these complications.

Therapeutics.—The most important factor is the diet. In almost all cases this requires modification, generally diminution or discontinuance of farinaceous food according to the age, and increase of the fat. The latter presents difficulties chiefly among the poor who are unable to afford cream or who live under such conditions that milk and cream undergo much bacterial contamination. Under such circumstances, the deficiency may be supplied by any oil or fat which is easily assimilated. Cod-liver oil is commonly used, but other oils, such as cotton-seed oil and olive oil, have been used; and apparently it makes little difference how the fat is supplied provided it can be digested.

There are many palatable emulsions of cod-liver oil, and any of these may be used, but it may be more convenient to use the plain oil. In either case the amount of oil given at each dose should not exceed 15 minims (1 cc.) for an infant six months old; 20 minims (1.25 cc.) for an infant twelve months old; and 25 to 30 minims (1.5 to 2 cc.) for an infant of eighteen to twenty-four months; these doses should be given three times daily just after food. In some cases, one of the combinations of malt extract with cod-liver oil is taken better and may be more valuable, especially where some farinaceous food is being allowed. A valuable method of administering fat is to add to the diet daily the yolk of one egg. This contains 20 to 30 per cent. of fat. It must be given very lightly boiled, otherwise it becomes indigestible. An infant of nine months can have half the yolk of one egg daily, at ten or eleven months the whole of the yolk can be given. After the age of twelve months, the egg can be given in the form of custard.

In some parts of Europe, especially in Vienna, but also in America by Jacobi, phosphorus has been strongly advocated. Opinions are much divided as to its value; some writers state that it is not only entirely without effect but that it produces gastro-intestinal disturbance and occasionally serious toxic symptoms. It seems probable that some, at least, of the benefit which has been attributed to phosphorus, may have been due to the oil in which it has almost invariably been given. It is usually dissolved in cod-liver oil or given in an emulsion with almond oil; $\frac{1}{200}$ to $\frac{1}{100}$ grain (0.3 to 0.6 mg.) of phosphorus may be dissolved in 1 dram of cod-liver oil (4 cc.), and half this quantity given two or three times a day. Jacobi recommends the elixir phosphori of the U. S. Pharmacopœia; of this, 6 to 15 minims (about 0.4 to 1 cc.) should be given three times daily.

Various organic and other compounds of phosphorus have been used, particularly lecithin, preparations of hypophosphites in syrup, wheat phosphates, the soluble part of bran, and many patent preparations containing phosphorus. The syrupus ferri phosphatis of the British Pharmacopœia is used by many for rickety children over the age of twelve months; it is given in doses of $\frac{1}{2}$ to 1 dram (2 to 4 cc.). Glycerin extract of bone-marrow has given good results in some cases. Various organic remedies have been tried, but, in most observers' hands, have proved useless.

The value of baths is perhaps hardly sufficiently recognized; the child should have a warm bath at about 85° F. every morning, and while

sitting in the bath should be douched with water at a slightly lower temperature, 75° to 80° F. If this is done with tact and the child gradually accustomed to it, there should be no dislike to it, and it seems to have an invigorating and tonic effect which may be of value especially in reducing the nervous instability.

If convulsions have already occurred, or if a tendency to them is shown by the presence of laryngismus stridulus, tetany, or facial irritability, bromide should be given with cod-liver oil. Two to 4 grains (0.13 to 0.26 gm.) of potassium bromide in 1 dram (4 cc.) of cod-liver oil emulsion, are given three times daily. Sometimes chloral $\frac{1}{2}$ to 2 grains (0.032 to 0.13 gm.) is more effectual than bromide, and may be given every four to six hours.

Massage has been advocated and is likely to be useful in maintaining the nutrition of the muscles while it is necessary to keep the child off his feet; but it must be extremely gentle and is less applicable to infants under twelve months than to those who are older.

The child must be kept off its feet during the active stage, and if fat and heavy, and especially if the bones of the legs already show bending, this measure may be necessary for several months. Often the only way to insure this is to apply long splints to the outer side of the legs, the splints being sufficiently long to project well beyond the sole of the foot. They should be removed when the child goes to bed so that it may kick its legs about freely and exercise its muscles as much as possible.

Congenital Rickets.—It seems certain that rickets may be present at birth, but until recently cases of achondroplasia were described as fetal or congenital rickets, and, as Ballantyne has shown, there are several types of bone disease which occur *in utero*, all of which have probably been described as rickets in the past. The relation of these to rickets is uncertain, but they bear so little resemblance to postnatal rickets, that it seems wise at present to consider them as something altogether distinct, although, as Ballantyne suggests, it may be that rickets occurring during intra-uterine life, would be modified according to the period of development at which it occurred.

As to the frequency of congenital rickets, there is a wide discrepancy in statistics. Feyerabend at Königsberg, among 180 newborn infants, found 68.9 per cent. rickety. Schwarz in Vienna found that among 500 newborn infants, 80.6 per cent. showed rickets. Fede and Cacace, at Naples, among 500 newborn infants, found only 1 with clinical evidence of rickets, and in another series of 475 newborn infants, Fede and Finizzio found only 3 with rickets. Personal experience at the Children's Hospital, Great Ormond Street, suggests that within the first two months after birth rickets is excessively rare.

The symptoms are those which have already been described as characteristic of postnatal rickets, but the frequency of fractures in the long bones is a notable feature of the congenital disease. Often 4 or 5 of the bones are broken and the fracture is often complete, not greenstick.

Monti quotes Chaussier as having found in 1 case 42, in another

112 fractures. These are certainly not always produced during parturition for they have been found already united or in process of uniting at the time of birth (Notta). All degrees of curvature of bones are also found. It has been stated that the rachitic distortions of the thorax are lacking in this form, but this is perhaps doubtful, for H. Ashby has recorded a case in which the typical deformity of the rachitic chest was present at the age of fourteen days in association with several fractures in the limbs. Infants with congenital rickets are often of premature birth and apart from this are commonly feeble, so that the prognosis must be guarded. But so far as the fractures are concerned, the outlook is good; they unite rapidly after birth. With suitable feeding the rickets rapidly improves and may even disappear entirely in a few months.

There has been extensive failure of ossification of the skull in several of the recorded cases, a defect which some have described as *craniotabes*. It is very doubtful, however, whether such a condition bears any relation to the localized patches of *craniotabes* mentioned as characteristic of ordinary rickets where the thinning of the skull is probably due to absorption rather than to defect of formation of bone.

Congenital rickets is no doubt dependent upon some deficiency in the mother's blood of the constituents requisite for bone formation, and it is an observed fact that in a considerable proportion of the cases the mother has been ill during pregnancy. That the mother's health may exercise some effect, especially upon bone formation, in the fetus, is suggested by some experiments on rabbits in which the inoculation of the parents with the toxins of diphtheria or tuberculosis resulted in deformities of the hind limbs in the offspring (Charrin and Gley).

Treatment.—This, apart from suitable fixation for the fractured bones, consists chiefly in careful feeding, at the breast if possible, otherwise with milk which has been carefully modified so as to contain a proper proportion of fat.

Late Rickets.—Rickets is occasionally seen as an active disease in the later period of childhood and in adolescence, and has then been described as late rickets, *recrudescent rickets*, or *rachitis tarda*. Probably the term *recrudescent rickets* most accurately describes the majority, for usually the patient has shown evidence of rickets within the first two years of life and then after years of quiescence the disease has again started into activity. Much more rarely rickets makes its first appearance at this later period. Whether *recrudescent* or not, this late rickets is very rare; but it is said by some surgeons that adolescents at the period of rapid growth not infrequently show slight bending of bones, and this has by some been described as rickets. Apart from the curvature of bones, such cases usually show no other evidence of rickets and it seems very doubtful whether a mere failure of the hardening process in bone to keep pace with the rapid growth of bone at this age should be considered evidence of rickets. There is no doubt that bending of bones resembling that seen in rickets may occur quite apart from the histological characters of rickets. Stoeltzner produced bending of limbs in puppies by a special diet, but microscopic examination showed that the changes were not those of rickets.

Late rickets has occurred most often between the age of nine and fourteen years, but it has begun as late as seventeen years. At what age rickets should be described as late, has not been settled. Probably the disease beginning or recrudescent after the age of four years, might properly be described thus.

Symptoms.—These are similar to those already described, but the onset has usually been with some pain in the limbs, more or less severe, especially in the legs. At the same time there has been weakness so that in some cases the patient has been unable to walk without assistance. The ribs become beaded and the epiphyses enlarged, as may be seen in Fig. 54, of a boy, aged nine and three-fourths years, in whom the symptoms of rickets, after remaining almost quiescent since his earliest years, became active again at the age of nine and one-half years. He was under the care of my colleagues, R. Hutchison and A. E. Garrod, at the Children's Hospital, Great Ormond Street. There was no enlargement of the head in this case, and this appears to be the rule; only 1 case has been recorded in which the head became enlarged during late rickets (James).

The thorax has become distorted in some cases with deformity described as typically rachitic. The bending of the lower limbs is sufficient generally to cause a waddling awkward gait. With the *x*-rays, the bones give a less marked shadow than normal, presumably from deficiency of calcification.

Examination of the urine in one case (James) showed excessive excretion of lime (more than twice the normal). The amount of phosphoric acid was fully up to the normal but hardly excessive. Irregular pyrexia was noted in one case (Cautley) during the progressive stage.

Like rickets at an earlier age, the late form of the disease hinders growth and development, the establishment of puberty may be delayed, and the child remain undergrown. Hitherto no explanation of these cases of late rickets has been found. It has been stated in some cases that there was no obvious fault in the diet; in some cases a severe illness has preceded the onset.

Prognosis.—This must be guarded, for the deformity is often considerable; the disease is, however, rarely fatal. There seems to be less tendency to respiratory complications than in rickets during the first two years of life.

FIG. 54



Treatment.—The treatment which has been found most effectual is similar to that used in ordinary rickets, namely, the administration of cod-liver oil, to which some have added phosphorus. After the disease has become quiescent, operative measures may be required for the correction of deformities, or apparatus, such as steel supports or splints, may be necessary to prevent further bending of the long bones.

CHAPTER XXI

SCURVY (SCORBUTUS)

By ROBERT HUTCHISON, M.D., F.R.C.P. (LOND.)

SCURVY may be defined as a general disorder of nutrition characterized by debility, mental apathy, and anemia, with sponginess of the gums, ulceration of the mouth, and a tendency to hemorrhages into the subcutaneous tissues and from mucous surfaces.

History.—Scurvy does not seem to have been clearly recognized in Greek and Roman times, and the earliest description of the disease as we now know it dates from the year 1260. It prevailed extensively on shipboard until 1795, when, after the introduction of lime-juice, it rapidly declined, and is now rare, only 22 cases having been treated in the Seamen's Hospital at Greenwich in the last ten years.

Etiology.—The causation of scurvy is still obscure, but it is now generally agreed that it is due to the absence of some ingredient in the diet. The view that the disease is caused by poisoning with ptomaines, which was brought forward by Forup and supported by Jackson and Vaughan Harley, is not generally accepted, nor has the infective theory gained many supporters. As to the nature of the defect in the diet, we are still in the dark. The hypotheses that it consists in a deficiency of potash salts (Alfred Garrod) or of alkaline compounds (Wright) have failed to stand the test of criticism, and it is now generally believed that scurvy is brought about by the absence from the diet of a "vitamine" of unknown nature, just as pellagra and beriberi appear to be. Axel Holst has succeeded in producing the disease artificially in animals and has carried out many experiments which favor the "vitamine" view. The exact nature of the vitamine has not, however, been determined. Although present in fresh vegetables it disappears when they are dried even *in vacuo*; it is absent from dried grains, but appears when they are allowed to germinate, while it persists in lime-juice even when boiled.

Morbid Anatomy.—The bodies of patients who have died of scurvy usually exhibit only a slight degree of rigor mortis, and putrefaction occurs early. The only constant morbid change found is effusion of blood in various situations. These effusions, which may be diffuse or circumscribed, are met with both in the skin and subcutaneous tissues and under the periosteum of the bones. They consist of altered blood which may have undergone partial clotting or even organization into fibrous tissue. Hemorrhages are also met with in the pleura and pericardium and, though more rarely, in the peritoneum as well. There may also be hemorrhagic effusion into the joints. The internal organs show no constant change, but the heart muscle is soft and often degenerated. The lungs are œdematous, and may contain infarctions. The kidneys

and liver rarely exhibit any signs of disease. The spleen is large, soft, and congested, and may also show infarcts on its surface. It is important to note that all accurate observations agree in showing that the bloodvessels exhibit no gross or microscopic changes.

In the altered gums, Babes distinguishes five layers: (1) A surface layer, for the most part free from epithelium, moderately thick, pale, resembling a diphtheritic membrane with a few fragments of nuclei, and containing various bacteria, especially streptococci. (2) A structureless layer, about one millimeter thick, consisting of a felt-work of long fine bacteria. (3) Uni- and multinucleated round cells. (4) A layer of oedematous mucous membrane containing many bacilli resembling those in the second layer. In the walls of the vessels are numerous swollen spindle cells. (5) Large and much dilated vessels with large spindle cells in their walls. In the blood which fills the vessels are various cell masses, numerous multinucleated leukocytes, endothelial and mast cells but no bacteria.

Symptoms.—Prodromal Symptoms.—Scurvy is usually a disease of insidious onset. The patient begins to suffer from loss of bodily vigor, and from an even more marked mental apathy and lassitude so that the slightest task becomes a burden. At the same time he looks ill. The face becomes pale, or sallow and drawn, the eyes sunken, lustreless and encircled by dark rings. At this period, too, there may be some pitting of the ankles on pressure and a tendency to diarrhoea, while it may be observed that the least knock or injury tends to be followed by a bruise. He suffers also from pains in the limbs and joints. To these symptoms there are soon added those characteristic of anemia—shortness of breath on exertion, palpitation, and a tendency to syncope.

Such symptoms may precede by a few days or even weeks the more characteristic signs. Among these the most striking, though not necessarily always present, are the changes in the mouth. The gums begin to swell, especially around stumps or carious teeth, and as the process goes on the swelling may become so great as to amount to a veritable hypertrophy, so that the teeth become buried in a mass of soft, fungous tissue of a bluish or purplish tint. Ulceration quickly follows along the margins, the process being accompanied by the discharge of a sanious fluid which imparts an odor of great fetor to the breath. Finally the teeth become loosened in their sockets and may fall out, while necrosis of the alveolar edges ensues.

Equally characteristic and constant are *hemorrhages into the skin and subcutaneous tissue* which assume the form either of petechiæ or of ecchymoses. The former occur as small red or purple spots resembling flea bites which appear first around the hair follicles of the lower extremities and impart, by the elevations which they produce, a slight feeling of roughness to the skin. They remain for about a week, and then gradually fade into greenish spots which soon disappear; their disappearance being followed by a slight degree of desquamation. The production of the petechiæ is determined by the slight irritation caused by the friction of the clothes, and hence they are always to be found first on the outer surface of the leg, and the outer and anterior aspects of the thigh. Here

and there the petechiæ may coalesce into larger areas or maculæ. In severe cases the slightest pressure on the skin is sufficient to cause ulceration, the ulcers having thick edges and bleeding surfaces with offensive discharge. Such ulcers may spread rapidly and invade surrounding tissues, giving rise in some cases to dangerous, and even fatal hemorrhage. Ecchymoses, the other characteristic surface lesion of scurvy, are produced by hemorrhage into the subcutaneous or intermuscular tissue. They may occur spontaneously or as the result of injury, and vary greatly both in size and extent, being commonest in the lower extremities, where they may form quite large swellings. The part affected by them is brawny, tender, and pits on pressure, the indentation persisting longer than it does in ordinary cedema. The skin over them is red, shiny, and hot. Such effusions are common, also, in the popliteal space and in the bend of the elbow, as well as in the loose tissue around the malleoli, and beneath the muscles of the jaw. In these situations they form indurated swellings which fill up the natural hollows of the part, and greatly interfere with the movements of the adjacent joint. Where such effusions occur over the shins, they are apt to be mistaken for syphilitic nodes.

There is no marked tendency to bleeding from the internal organs but hemorrhages may take place from the mucous surfaces. Of such hemorrhages, epistaxis and bleeding from the mucous membrane of the mouth are commonest. Bleeding may also occur from the mucous membrane of the intestine when there is a coexisting diarrhœa. Hemoptysis, hematemesis, and hematuria are rare. Hemorrhagic effusion into the pleura and pericardium has also been described. Not uncommonly hemorrhage occurs under the conjunctiva, and may be so extensive as appreciably to raise the ocular layer, leaving the cornea at the bottom of a pit surrounded by swollen and red conjunctival membrane.

As the disease progresses anemia becomes a marked feature. The *blood* presents the characters of a secondary anemia, and there is no leukocytosis unless secondary inflammatory complications exist. Special interest attaches to the chemical condition of the blood, on which, however, but few observations have been made. If the views of Ralfe and of Wright as to the etiology are correct one would expect to find a diminution of alkalinity and of coagulability, and Wright in a few cases has shown that diminution of coagulability is present. Barnardo, who had the opportunity of investigating this point during the Somaliland Campaign, found no constant relation between the degree of reduced alkalinity and the severity of the symptoms. However, he states that in all cases where the alkalinity is much reduced, profound constitutional disturbance will soon manifest itself if it be not already present.

Alimentary symptoms are often absent. Appetite is not necessarily impaired, but dyspeptic symptoms may be present as the result of the imperfect diet which produces the disease. Constipation is the rule, but the conditions under which scurvy is developed frequently favor the production of diarrhœa of a dysenteric type, and when such a complication exists it may be attended by bloody discharges from the bowel.

The *urine* at the outset is scanty, high-colored, turbid, and occasionally

albuminous, but as improvement sets in it becomes more abundant and pale. The amount of free acid in it is diminished, and so, it is alleged, are the potash salts.

Of the *complications*, gangrene of the lung is one of the most frequent and dangerous. It is marked by the usual expectoration of dark fetid matter, by rapid and difficult breathing with great depression, and usually ends fatally.

Buzzard describes an affection of the chest in scurvy which may be mistaken for pneumonia. Faint rigors, followed by a certain amount of feverishness and accompanied by lancinating pain in one or both sides, usher in this condition. The pain is felt only in coughing, and a very viscid mucus is expectorated. The dyspnœa increases, and a constriction, as though from a cord bound tightly around the chest, is described. Although it occasionally happens that these pulmonary symptoms are dependent upon true inflammation, they are much more commonly associated with the effusion of sanguineous fluid into the cavity of the pleura or into the substance of the lung itself, these structures sharing that tendency to effusion which is the dominant feature of scurvy. When the lung is thus invaded the expectoration after a short time becomes dark and sanious, with all the horrible fetor which is ordinarily associated with gangrene of the lung, but which is here dependent upon decomposition of the bloody fluid poured into the lung substance. There are cold sweats, increasing dyspnœa and anxiety, a small and frequent pulse, and death. In other cases there is no pain or cough, but the breathing rapidly becomes short and labored, and death occurs suddenly. Auscultatory signs in the lungs are usually wanting, but now and then there is localized dulness on percussion with bronchial breathing, or mucous rales are heard, sometimes also with gurgling sounds at certain parts of the chest.

Night blindness is a condition sometimes met with in patients suffering from scurvy who have also been much exposed to bright light, and may occur quite early in the disease. It would appear to be merely the result of the anemia and exhaustion which scurvy produces, and is in no sense an essential part of the scorbutic process.

Diagnosis.—If all the characteristic symptoms are present and if the disease arises simultaneously in a number of subjects in circumstances known to favor its development, the diagnosis is easy. Difficulty only occurs when one has to deal with sporadic cases, such as the cases of land scurvy occasionally met with in badly fed individuals.

The disease which perhaps most closely resembles it is *purpura hemorrhagica* (*morbus maculosus* of Werlhof), but in this the affection of the gums is absent and the hemorrhages have not, as they have in scurvy, an inflammatory character. *Mercurial cachexia*, which in many points closely simulates scurvy, is now but rarely seen and an inquiry into the history will usually lead to a correct conclusion. *Acute lymphatic leukemia*, which is often marked by ulceration in the mouth, can be distinguished by an examination of the blood.

Prognosis.—This, except in the severest cases, is favorable, provided suitable treatment can be adopted. It has often been noted that the

outlook is by no means dependent upon the severity of the lesions in the skin, mouth, and muscles, but is in far closer relation to the state of the internal organs such as the lungs and heart. The supervention of the complications and of intercurrent disease also exerts a powerful influence upon the prognosis while a speedy and often unexpected fatal result may be brought about by severe hemorrhage or heart failure. Even in cases which run a favorable course it may be weeks or even months before the patient is restored to his original vigor, and when recovery is complete there may still be some results shown in cicatrices in the skin or partial ankylosis of joints.

Treatment.—The first point is to remove the patient if possible from the place in which the disease has developed and to bring him under more hygienic conditions. Cold and damp should especially be avoided and he should be placed in warm and dry surroundings. Of even greater importance is it to make a radical alteration in his diet. Whatever view may be held as to the causation of the disease, all experience goes to show that the introduction into the diet of a sufficient quantity of fresh vegetable food has a powerfully curative effect.

It would appear that there is no particular form of vegetable food which has a specific influence over the disease, but that all are equally efficacious. The antiscorbutic power of fresh limes and lemons has been known since the seventeenth century, and these fruits still constitute a favorite remedy. It is important that they should be fresh; lime juice which has been bottled for some time is apt to decompose into free citric acid and carbonates and loses much of its value. An objection to lime juice is its rather acrid taste, on account of which it is sometimes found to be difficult to induce those who are exposed to the disease to take it regularly as a preventive. Lemonade made from fresh lemons is not open to this objection.

Preserved vegetables, though useful, seem to have a feebler antiscorbutic power than fresh; sauerkraut appears to be more serviceable in preventing the disease than any other form of preserved vegetable, and Captain Cook employed it successfully in some of his voyages. Infusions of malt are also powerfully antiscorbutic. Forster, who accompanied Cook in his second voyage, describes a severe outbreak of scurvy and its cure by infusion of malt without any other change in the diet. In some of the worst cases the patient took as much as five pints of the infusion in a day. The infusion should be fresh, for its good qualities are impaired if it is allowed to become damp and mouldy.

Fresh meat juice has been found to be of value as an antiscorbutic, owing, it is alleged, to the lactates which it contains. Milk is also serviceable, three pints of it containing as much citric acid as one ounce of lime juice, and instances are on record of outbreaks of scurvy which have been checked by its administration. Of beverages, French and Italian wines are stated to be antiscorbutic, but opinions as to the power of cider in this respect vary considerably.

Drugs are of far less use than the measures above indicated. Wright, on hypothetical grounds, has recommended the administration of Rochelle salt in doses of 30 to 60 grains (gm. 2 to 4) thrice daily until

the urine is alkaline, along with 20 grain (gm. 1.3) doses of crystallized calcium chloride to increase the coagulability of the blood. Barnardo speaks favorably of this treatment as the result of his experience in Somaliland. The administration of bitters—especially of quinine—and of iron to combat the anemia is of help in restoring health, and special complications may require appropriate remedies.

Locally the conditions of the mouth will demand most attention. Antiseptic washes of permanganate or chlorate of potash or peroxide of hydrogen help to remove the feter, while the spongy and ulcerated gums may be painted with a strong solution of nitrate of silver. Absorption of local effusions of blood may be promoted by gentle massage.

The *prophylactic treatment* consists in attention to general hygienic conditions and in the provision of an abundant and varied dietary containing an adequate proportion of vegetables. In Nansen's Arctic expedition, which lasted three years, and during which scurvy was entirely avoided, the diet consisted of meat of various sorts in hermetically sealed tins, dried fish, potatoes both fried and tinned, all sorts of dried and preserved vegetables and fruits, jam, marmalade, condensed milk, preserved butter, and desiccated soups. Flour was carried to make fresh bread. Drinks consisted of tea, coffee, cocoa, beer, and lemonade.

Lime juice has long been used as a prophylactic but is apt to undergo decomposition when kept long in a barrel. Two ounces twice a week is recommended as a preventive dose.

INFANTILE SCURVY

That infantile scurvy is closely related to the adult form of the disease there can be little doubt. None the less, the clinical manifestations of the two forms are very different, but the differences are probably to be explained by differences of diet and by the anatomical and physiological peculiarities of the infantile period of life.

History.—Infantile scurvy was really described by Glisson in his *Treatise on the Rickets* published in 1651, but the disease was lost sight of for two centuries when it was again described by Continental writers under the title of "acute rickets." Cheadle first pointed out its identity with adult scurvy in 1878, and five years later Barlow secured general recognition for the truth of Cheadle's views by an elaborate paper, which has become a classical publication on the subject, and which has caused infantile scurvy to be generally known on the continent of Europe under the name of "Barlow's disease."¹

Etiology.—Clinical observation shows that the vast majority of cases of scurvy arise in infants who are being fed on a diet which is deficient in *fresh* constituents. The diet which most commonly produces the disease seems to be one consisting of condensed milk with the addition of a tinned food, but a diet of sterilized milk alone is undoubtedly

¹ *Trans. Royal Medical and Chirurgical Society*, 1883, lxvi, p. 159.

capable of giving rise to it, and so even may milk which has merely been boiled. Griffith,¹ in summarizing the results of an investigation of 356 cases collected by a committee of the American Pediatric Society, with the addition of 18 cases of his own, concludes that in 60 per cent. a proprietary food had been used but often with the addition of sterilized milk. Nine per cent. had been fed on condensed milk and 19 per cent. on sterilized milk only.² Pasteurized milk seems much less apt to produce the disease. That the want of freshness in the food is not the *only* cause of the disease, however, seems to be shown by the fact that 10 of the cases had been fed on the breast only and several on raw milk.

The nature of the substance which is absent from a scorbutic diet is unknown, but it will probably prove to be a so-called "vitamine," just as in the adult form of the disease.

Morbid Anatomy.—The chief changes in infants who have died of infantile scurvy are present in the neighborhood of the bones. If a section be made across a limb which has been the seat of swelling during life it will be found that the periosteum is thickened, highly vascular, and separated from the subjacent bone by a layer of blood clot which may show various degrees of organization. There is, however, no sign of inflammation, and, as a rule, no hard bone is formed in the periosteum except in very old-standing cases. The muscles surrounding the bone may be infiltrated with blood or serum, which gives them a sodden appearance. The bone itself exhibits a considerable degree of rarefaction, the cancellous tissue being unusually porous and the normal marrow replaced by a highly vascular connective tissue into which hemorrhages may have occurred. The changes characteristic of rickets may also be present in the bones. The rarefaction of the bone is apparently the result of delayed ossification and is the cause of the fractures not uncommonly met with in severe cases and which are usually situated a little above the epiphyseal line, although there may sometimes be separation at the line of the epiphyseal cartilage itself.

Hemorrhagic effusions may be met with elsewhere in addition to those around the bones, such as in the joints or in the serous cavities or subdural space. None of these, however, is characteristic of the disease. The internal organs exhibit no constant change.

Symptoms.—Scurvy is commonest in infants of about eight to ten months old. In an analysis of 64 cases by Bovaird³ the youngest was six months old, the oldest two and a half years, the average age being twelve months. Fifty-four per cent. of the cases occurred between the ninth and thirteenth months. The children affected are usually well-nourished, but often exhibit some degree of pallor. The invasion may be either gradual or abrupt. After a few days of fretfulness or after having exhibited for some time great tenderness when handled, the more prominent symptoms appear. The most striking of these is

¹ *New York Medical Journal*, 1901, lxxiii, p. 317.

² For additional evidence of the production of scurvy by sterilized milk, see Netter, *Rev. des Maladies de l'Enfance*, 1902, xx, p. 543; Neumann, *Deut. med. Woch.*, 1902, xxviii, pp. 628, 647; and Ashby, *Brit. Med. Jour.*, 1904, i, p. 479.

³ *Philadelphia Medical Journal*, 1898, ii, p. 375.

tenderness of the legs, which causes the child to scream out when touched or even at the approach of the doctor. It can be observed that the child lies very still, usually on his back with one or both legs everted and motionless. Examination in a well-marked case reveals some swelling of the bones, most commonly of the lower end of the femur or upper end of the tibia. The long bones of the upper extremities are much more rarely affected, the collective investigation in America yielding only 14 cases with swelling in the arms, to 131 in which the legs were affected. At the site of these swellings the tenderness is extremely acute and the skin over them is often tense and glossy, and may be slightly œdematous, but there is no local heat. On gently handling the limb soft crepitus may be elicited, from fracture or separation of the epiphysis. In some cases hemorrhage takes place into the orbit, giving rise to proptosis and ecchymosis of the eyelids. This symptom occurred in 49 out of 379 of the American cases. The proptosis may appear suddenly, often during a fit of crying, and in severe cases may even lead to ulceration of the cornea.

Rarer sites of hemorrhage are around the ribs, clavicles, or bones of the skull. Sir Thomas Barlow has described a peculiar depression of the sternum *en bloc*, which is present in severe cases and is apparently due to a loosening of the articulations between the sternum and ribs.

Changes in the Gums.—These are not usually present unless some teeth have been cut, but even in the absence of the latter there may be a slight degree of injection and ecchymosis, especially over the sites of the incisors. Should any teeth have erupted, the gum around them is usually swollen and of a purplish color, but the change is rarely if ever so marked as in the scurvy of adults and does not often go on to ulceration. It is rare for the gums to appear normal after any teeth have appeared, but a few such cases have been observed.

Other Symptoms.—Petechiæ and subcutaneous ecchymoses are rarely met with in infantile scurvy and hemorrhages from mucous surfaces, with the exception of the gums, are not common. Hematuria is met with not infrequently and a slight degree of it, at least, is probably much commoner than is generally believed. Sometimes it is the only symptom present and in a few cases it appears to lead to nephritis¹ or pyelitis. Fever is not a conspicuous feature, but when extensive hemorrhages have taken place there may be a rise of temperature, which, however, rarely exceeds 101° or 102° F.

Changes in the Blood.—There is usually a greater or less degree of anemia, especially in cases in which extensive subperiosteal hemorrhages have occurred. The anemia is usually of the chlorotic type, the hemoglobin being reduced out of proportion to the red cells, but where the hemorrhages have been especially severe the characters of a secondary anemia may be exhibited as well, and the red cells are reduced in number and some nucleated forms present. In the absence of complications no leukocytosis occurs. The chemical changes in the blood have not been fully investigated, but in a series of cases examined by the writer no

¹ See Still, *Lancet*, 1904, ii, p. 441.

alteration in the coagulability could be discovered. Whether or not there is any reduction of alkalinity has not been determined.

Association with Rickets.—The relation of scurvy to rickets has been much disputed. That the two conditions are not invariably associated is shown by an analysis of 40 fatal cases by Schoedel and Nauwerk,¹ in 18 of which the presence of rickets had been recognized during life, while it was found in 3 others after death. The frequent coexistence of rickets in cases of scurvy would seem indeed to be due merely to the fact that the kind of diet which produces the one disease also tends to give rise to the other.

Diagnosis.—This is easy in a well-marked case provided the leading features of the disease are known to the observer. The screaming of the child on examination, the swelling and tenderness of the legs, and the condition of the gums leave no doubt as to the nature of the affection with which one has to deal. All cases, however, are not so pronounced in type. Not infrequently one encounters mild or incipient forms which it is easy to overlook. In these, tenderness when the child is handled or when he is put in his bath may be the only symptom. In other cases again, slight sponginess around the incisor teeth may alone be present or one may have to deal with an apparently causeless hematuria. In any case in which there is doubt two points will help. One is the nature of the feeding. If this has been of such a nature as is known to favor the development of the disease the diagnosis will be greatly strengthened. The other point is the application of the therapeutic test. If the symptoms present are really due to incipient scurvy then they will certainly disappear rapidly so soon as appropriate treatment is begun; if they fail to do this then one has to do with some other condition.

The affections for which scurvy is most often mistaken are these:

1. *Rheumatic Fever.*—Time and again the writer has had well-marked cases of infantile scurvy sent to him with this diagnosis, and in one such case the affected limb had been painted with iodine, with the result of greatly aggravating the sufferings of the child. The mistake should never be made if it is remembered that below the age of one year rheumatic fever is practically never met with.

2. *Periostitis.*—The distinction between scurvy and periostitis is often a matter of great difficulty, especially when the gum changes are absent. The presence of a marked degree of pyrexia is in favor of a diagnosis of periostitis, for in scurvy, fever is usually absent or but trivial in amount. If the other signs of scurvy are present as well, the diagnosis is clear, but sometimes one may be obliged to fall back on the therapeutic test.

3. *Infantile Paralysis.*—When infantile paralysis sets in, as it sometimes does, with a marked degree of hyperesthesia, it may simulate scurvy. There is no swelling of the affected limb and the other signs of scurvy are absent.

4. *Epiphysitis.*—Epiphysitis may simulate scurvy but the swelling in the latter extends along the shaft of the bone and is not confined to the neighborhood of the epiphysis.

¹ *Rev. des Maladies de l'Enfance*, 1902, xx, p. 543.

5. The changes in the mouth may be mistaken for those of ordinary *ulcerative stomatitis*. In scurvy the changes are confined to the gums, while in stomatitis they extend to the lips and cheeks as well. The ulceration in the mouth which often occurs in *acute leukemia* may lead to a suspicion of scurvy. Here the examination of the blood will at once settle the diagnosis.

6. Cases which are characterized by hemorrhage into the orbit may be mistaken for *sarcoma of the skull* or for *chloroma*. In the former case there are usually signs of sarcoma elsewhere and in the latter the blood shows an excess of lymphocytes while in both the positive signs of scurvy are absent.

7. The *hematuria* of scurvy is apt to be mistaken for renal hemorrhage from other causes, such as renal sarcoma. In a doubtful case of bleeding from the kidney it is therefore always well to try the effect of an anti-scorbutic diet before proceeding to other measures.

Prognosis.—This is quite favorable, provided the disease is recognized in time and suitable treatment adopted. Nothing in therapeutics is more striking than the rapidity with which such patients improve under a change of diet, although some degree of thickening of the bones may persist for a long time. Death, when it occurs in the more severe cases, is usually the result of intercurrent diseases, of which bronchopneumonia and chronic diarrhœa are the most frequent, although sudden hemorrhage, cardiac failure, or exhaustion may occasionally lead to a fatal issue.

Treatment.—This consists solely in altering the diet. Tinned food and sterilized milk must be stopped at once, and the child put upon a due allowance of unboiled milk. Fruit juice should be added, a few teaspoonfuls of grape or orange juice sweetened with a little sugar being given daily. Baked potato is also useful, a little of the part under the skin being rubbed up with the milk into a thin cream, which is either added to the bottle or given separately (two teaspoonfuls three or four times a day). Raw meat juice is of value, and may be given in quantities of half an ounce daily. Drugs are of little service, though the vegetable salts of potash exert a certain curative influence. During the period of convalescence cod-liver oil and iron are helpful.

Scorbutic infants should be handled carefully and the clothing should be so constructed that it can be easily taken off and on. If it is necessary to move the child about he should be placed on a pillow. The affected limb should be steadied by light splints or wrapped in wet towels, which, if allowed to dry in position, afford considerable support. In mild cases a casing of cotton wool secured by a light bandage is sufficient protection.

PART VI

DISEASES OF THE RESPIRATORY TRACT

CHAPTER XXII

THE MECHANICS OF RESPIRATION AND OF THE RESPIRATORY DISEASES

By THOMAS R. BROWN, M.D.

Introduction.—In discussing the mechanics of respiration and respiratory diseases, the wisest course seems to review briefly the mechanism of physiological respiration and follow this with as complete an exposition of the mechanics of the various pathological conditions of the respiratory tract as is possible in the limits of such an article, considering in the first place the various impediments to respiration, in the second place the effect such impediments have upon the respiration, and finally how and by what means the organism adapts itself to the new conditions.

Anatomy and Physiology of the Respiratory Tract.—The lungs may be considered as two large bags broken up into saccular divisions and subdivisions, finally consisting of little pouches or infundibula, the walls of which are hollowed out into alveoli. These alveoli are bathed in about 1.5 kilograms of blood, so that we may consider the air cells as being surrounded by a film of blood 10μ in thickness. The first branches of the bronchial trunk are given off at right angles, and all the bronchi are hyparterial except one branch on the right side. A band of muscular fibre surrounds the opening of the terminal bronchiole into the atrium, but beyond this no muscle is found, according to Miller. Cilia are present almost to the terminal bronchioles. The trachea shows a peculiar variation in that it is smallest just below the larynx, from which point its cross-section steadily increases until about the middle of the tube, whence it again decreases to its termination, and this peculiar variation is repeated in the bronchi; by this mechanism the air is made to enter with a rotatory motion.

Most of the nerves of the lung originate from the anterior and posterior pulmonary plexuses; they contain both vagus and sympathetic fibres, the former belonging mainly to the musculature, the latter to the blood-vessels. The principal masses of lymph glands occupy the space between the right and left main bronchi, while single glands are found surrounding the bronchi and lying on the pulmonary artery.

From 2000 observations Hutchinson gives the respiratory rate as from 16 to 24 a minute for the average man, while Vierordt gives 11.9 and Ruef 19.35. As to the rhythm of the respiratory movements the experiments made on Marey's pneumograph show, first, that inspiration passes into expiration without appreciable pause; second, that inspiration is shorter than expiration, the usual ratio being 5 to 6; and third, that the curves of inspiration and expiration differ in certain characters, the inspiratory phase is relatively shorter in women, children, and the aged and the respiratory rate and rhythm are affected by many factors: position, emotional disturbances, muscular activity, the time of day, etc.

For the pressure conditions existing within the lungs and pleural cavity, slightly different figures are given by different investigators. Due to the fact that the lungs are in a state of permanent distension within an air-tight cavity, the intrathoracic pressure is always negative under normal conditions, this negative pressure being, of course, greater during inspiration, less during expiration, and also being somewhat affected by posture. Under forced expiration, however, where the air passages are obstructed, the intrathoracic pressure may become positive, as for instance during a violent coughing attack when there is obstruction to the expiratory blast. The intrapulmonary pressure, on the other hand, varies with the phase of the respiration, being negative during inspiration, positive during expiration.

As to the volume of air respired, the figures usually given are that the tidal air equals 500 cc., the complemental air 1500 cc., the reserve or supplemental air 1240 to 1800 cc., the residual air 1230 to 1640 cc., and the stationary air 2470 to 3440 cc. The bronchial capacity is about 140 cc., while the alveolar capacity after quiet expiration equals from 2000 to 3000 cc., this, of course, being increased during inspiration and decreased during forced expiration.

In the admixture and purification of air in the lungs three important factors are concerned: first, the tidal movements, due to inspiration and expiration, and acting by the mere force of the air currents; second, the cardiopneumonic movements, due to the heart beat; and third, the diffusion of oxygen and carbon dioxide, depending upon differences in the partial pressure of these two gases in the various portions of the respiratory tract. As regards the interchange of the two gases between the alveoli and the blood, the belief is general that this is due both to physical and to chemical factors, diffusion being the most important, although it may be possible that the living tissues play an active part.

The Muscular Mechanism of Respiration.—To bring about the changes in the lungs which are known as inspiration and expiration, a mechanism is necessary to produce corresponding changes in the size of the thorax, for the lungs follow the thoracic movements because of the constant negative pressure in the pleural cavities and because of their perfect elasticity. Theoretically the thoracic movements might be brought about in any one of three ways: there might be an active inspiratory effort followed by passive expiration due to the elastic reaction of the thoracic and pulmonary tissues and to gravity, or there might be an active expiratory effort followed by a passive inspiration

due to the relaxation of the expiratory muscles, or both inspiration and expiration might be active, due to the contraction of certain sets of muscles. In reality the first of these types of respiration, that is, active inspiration followed by passive expiration, is the method under normal conditions. According to some observers there is a distinct pause after expiration before the next inspiration is inaugurated, while according to others this pause is only present under abnormal conditions.

The chief muscles of inspiration, that is, the muscles which play the most important rôle in enlarging the thoracic cavity, are the diaphragm, the quadrati lumborum, serrati postici inferiores, scaleni, serrati postici superiores, levatores costarum, external intercostals and intercartilaginei. The contraction of these muscles brings about an increase in the thoracic cavity in three dimensions by two processes, the elevation of the ribs and the descent of the diaphragm. The elevation of the ribs also brings about an increase in the transverse diameter of the thorax, while the corresponding shortening of the vertical diameter is more than counteracted by the fixation of the lower ribs and the descent of the diaphragm. This elevation of the ribs is brought about by the contraction of a number of muscles of which the external intercostals are probably the most important, although the scaleni, the serrati postici superiores and the levatores costarum play a rôle in this process.

By the contraction of the muscular fibres of the diaphragm, first a lowering of the diaphragm and second a flattening of its circumference takes place, the latter being far the more important of the two under normal circumstances. The contraction of the diaphragm may cause a widening of the lower portion of the thorax by pressing on the abdominal viscera and thus extending the abdomen and pushing out the lower ribs.

Quiet expiration is in all probability an absolutely passive process, although it is possible that the contraction of the internal intercostal muscles plays a part here; it is much more probable, however, that their chief function under these circumstances is to maintain the tension of the intercostal tissues. Under pathological conditions, due either to obstruction to the entrance of air in any portion of the respiratory tract or to poor aëration of the blood due to any other cause, many other muscles are brought into play both during inspiration and expiration. The accessory muscles of inspiration act mainly either by increasing the action of the inspiratory muscles described above or by furnishing them with more fixed supports from which to act. Thus the sterno-cleido-mastoid, the infra-hyoid, the pectorals, the trapezei and the rhomboidei muscles play an important part in labored respiration, aided further by the action of the erectores spinæ in extending the spinal column and by the lower slips of the serratus magnus. In forced expiration the most important muscles are those of the abdominal wall, which press upon the abdominal viscera, push the diaphragm upward, and pull down the sternum and ribs. In this depression of the lower ribs, the abdominal muscles are assisted by the serrati postici inferiores and by portions of the sacrolumbalis.

Under conditions of great obstruction to the inflow of air or in any case where the aëration of the blood is markedly hindered, and notably

in severe cases of asphyxia, many other muscles may be called into play both in inspiration and expiration—in fact, every muscle that can depress or elevate the ribs, exert pressure on the abdominal viscera or furnish fixed points for inspiratory or expiratory muscles.

Due to the inspiratory change of shape and size of the thorax produced by this muscular mechanism, the pulmonary movement takes place in two directions from two fixed points; vertically from the apex toward the base of the chest, so that during inspiration the lower border of the lung descends from the level of the sixth or seventh to that of the tenth or eleventh rib, and anteriorly from the mediastinal attachment of the lungs toward the front and the sides of the chest, so that the anterior margins of the lungs move forward and encroach on the cardiac dulness.

As regards the different types met with under normal circumstances, in men on quiet breathing the type is mainly diaphragmatic, while in women the costal type is met with in quiet breathing. According to most observers this difference in type is to be ascribed to difference in dress, as young children of both sexes as a rule have but one type of inspiration, the diaphragmatic. In labored respiration, however, these differences between the diaphragmatic and costal types of respiration in the main disappear, and all the ordinary respiratory muscles and in many cases the accessory muscles are called into play.

Besides the respiratory muscles described above, certain other sets of muscles come into play, which, although they exert no influence upon the size or shape of the thorax either directly or indirectly, nevertheless facilitate the free entrance and exit of air to and from the lungs; most of these play an important rôle when the respiration is labored, such as the laryngeal and nasal muscles, the latter movements being more marked in children and especially striking when there is marked obstruction to the entrance of air into the lungs.

The Nervous Mechanism of Respiration.—In order to appreciate the mechanics of the respiratory diseases it is quite as important to have a knowledge of the nervous as of the muscular mechanism. The coördinated rhythmical contractions must be initiated in some portion of the central nervous system; in other words, there must be a definite respiratory centre. The exact position of this centre has been the subject of much investigation. The motor cells of the cord which innervate the respiratory muscles are called into activity either by nervous influences derived from afferent or sensory fibres or from fibres originating in cells of higher portions of the nervous system by way of the pyramidal tract fibres. Experiments have definitely shown that the spinal centres of their own accord are able to initiate the rhythmic respiratory movements, and that this higher centre is situated above the lower end of the medulla oblongata. Flourens believed that this centre was a small area just below the apex of the calamus scriptorius, of pinhead size, and called by him the *noeud vital*, while according to Gierka the centre is situated in Krause's respiratory bundle, below and a little to the outside of the nuclei of the pneumogastric and glossopharyngeal nerves. Mislawsky places the nucleus in the formatio reticularis on each side of the median raphé, and Gad also believes that it is situated in this position. Although

a number of observers have denied the existence of the respiratory centre, nevertheless the recent experiments are conclusive, and we may conclude with Starling that "for the normal performance and coördination of the respiratory movements, the integrity of certain parts of the medulla oblongata situated on each side of the median line is necessary, and that therefore these parts are the respiratory centre," Reichert concludes that "each half of the respiratory centre may be supposed to consist of two distinct portions, one of which upon excitation gives rise to a contraction of the inspiratory muscles, the other to a contraction of the expiratory muscles," the former being also an accelerator, the latter an inhibitory centre.

According to Rosenthal the activity of the centre is automatic, although it is intimately dependent upon the condition of the blood, the discharges becoming more active if the free removal of gases in the lung is obstructed in any way and becoming less active in the reverse condition, while Pflüger and Dohmen have shown that the respiratory centre may be stimulated either by a decrease of oxygen or an increase of carbon dioxide in the blood going to it. Pflüger's theory as regards the action of the respiratory centre is an interesting one. He believes that, due to the metabolic changes constantly going on in the cells of the centre, groups of molecules are produced possessing an affinity for oxygen in a very high degree, and that it is these reducing substances which act as the excitants in respiration. Flik and Golstein have shown the marked effects of variations in the temperature of the blood, while many observers have shown the influence of various afferent nerves upon the respiratory rhythm and activity. It has also been shown that the centre can discharge rhythmically in the absence of any rhythmic afferent impulses, and therefore we may conclude that "the rhythmical discharges from the respiratory centre are due primarily to an inherent property of periodic activity of the nerve cells of this centre" (Reichert).

The Influence of Afferent Nerves on Respiration.—This is of such importance that a brief review of some of the theories held regarding it is necessary. Of all the afferent nerves the vagi alone are the ones that play a permanently important rôle in this connection. According to Rosenthal "the cause of respiratory rhythm is to be sought in the existence of a resistance to the passage of impulses from the centre to the respiratory muscles, an increase of the resistance to discharge serving only to make each discharge more forcible, but the interval between consecutive discharges longer," under normal conditions this resistance being diminished by tonic influences ascending from both lungs by the vagus nerves. According to Hering and Breuer the stimulation of the vagus is due to alternate contraction and expansion of the lungs, thus bringing about an automatic regulation of respiration, the expansion of the lungs sending inhibitory or expiratory impulses, its collapse sending inspiratory impulses up the vagi, thus exciting alternately activity of the expiratory and inspiratory centres. Most of the recent investigators oppose Rosenthal's views that the pneumogastric fibres in the lungs are purely inspiratory and call more and more attention to their expiratory functions.

Gad concludes that the only impulses travelling up the vagi are expiratory or inhibitory in nature; that these impulses are excited by the condition of distension of the lungs and are therefore present even at the end of normal expiration, being abolished only by a total collapse of the lungs, or, as Head puts it, the vagi act like the governor of an engine in economizing the labor expended and in preventing the centre from wearing out by excessive exertion. Meltzer believes that this nerve contains two sets of fibres, the inspiratory and the inhibitory or expiratory, differing in their time relations so that when stimulated together the primary effect is expiratory, the more lasting effect inspiratory. Although the vagus is the only afferent nerve of absolutely fundamental necessity for normal respiration, nevertheless many other afferent nerves have an influence on respiration; in fact, there are hardly any of these nerves the stimulation of which may not under certain circumstances bring about variations in the rhythm or in the activity of the respiratory centre, such as the glossopharyngeal, the trigeminal, and the cutaneous nerves. Rosenthal's experiments have shown that stimulation of the central end of the superior laryngeal nerve has an almost purely expiratory effect. Stimulation of the inferior laryngeal frequently causes an inhibition of inspiration sometimes associated with active expiratory movements. Excitation of the glossopharyngeal nerves brings about an arrest of respiration, the muscles remaining in the condition of contraction or relaxation in which they were when the stimulus was applied, and the stoppage lasting for about the time of the two or three preceding respirations. The object of this, of course, is to prevent the aspiration of food into the larynx. An arrest of respiration may also be brought about by stimulation of the olfactory branches of the trigeminal nerve, notably by the inhalation of noxious or irritating gases, in some cases a pure expiratory reflex taking place.

The stimulation of a number of other nerves of the body produces various effects upon the respiratory apparatus. Thus a gentle stimulation of most of the sensory nerves causes a quickening and increase in the inspiratory movements, while if the stimulation is marked enough to produce pain, respiration is mainly of an active expiratory type. The application of gentle stimuli to any of the abdominal viscera or to the splanchnic nerves brings about either an increase in the expiratory pause, or, more often, strong contraction of the expiratory muscles.

The Innervation of the Lungs and of the Respiratory Muscles.—The muscles moving the *ala nasi* are innervated from the seventh nerve; those opening the glottis from the accessory portion of the vagus; the diaphragm is supplied by the phrenic nerves derived from the cervical cord by the fourth and fifth cervical nerves, while the intercostal muscles are innervated from the whole of the dorsal cord. As to the innervation of the lungs, the nerves are derived from the pneumogastric, sympathetic, and upper dorsal nerves, many small ganglia being scattered along their path. The vagus in all probability supplies trophic fibres and secretory fibres for the mucous glands, while the sensory fibres for the trachea, larynx, and lungs are also derived from this nerve. The sympathetic nerves supply trophic as well as efferent vasomotor fibres. According

to some observers, however, there is no satisfactory evidence for assuming the existence of broncho-dilator fibres in the vagus.

It is of especial interest to understand thoroughly the innervation and the action of the bronchial muscle fibres because of the extreme importance of their contraction or dilatation in a number of pathological conditions, notably bronchial asthma and the various forms of bronchitis. A contraction of the smooth muscle fibres in the bronchi and bronchioles, whether large or small, has a threefold effect: first, a constriction of these tubes, second, a diminution of air space in the lungs, in other words, a decrease in volume of the whole lungs provided no compensatory circulatory changes take place, and third, an increased resistance to the entrance and exit of air to and from the alveoli. The question of whether or not the vagus exerts a constant tonic action on the bronchioles is one which as yet cannot be answered satisfactorily.

Accessory Respiratory Centres.—The existence of a number of subsidiary respiratory centres both in the brain and the spinal cord has been claimed by a number of investigators, as a polypnœic centre in the *tuber cinereum*, an inspiratory or accelerator centre in the optic thalamus, an expiratory or inhibitory centre in the anterior, and an inspiratory or accelerator centre in the posterior corpora quadrigemina, and an inspiratory or accelerator centre in the pons varolii and the nuclei of the trigeminal nerves, these centres in all probably not acting during normal respiration.

THE MECHANICS OF RESPIRATORY DISEASES AND PATHOLOGICAL CONDITIONS

Obstruction and Narrowing of the Respiratory Passages.—**Obstructions in the Upper Respiratory Tract.**—*Nose.*—Obstruction of the nasal passages may be brought about by a number of conditions, such as tumors, foreign bodies, fractures of the turbinate or nasal bones, hemorrhage, catarrh with thick secretions, hyperemic conditions of the mucous membranes, deflection of the septum, hypertrophy of the turbinate bones, and adenoids in the nasopharynx. If but one side is affected no harm is done, because each nasal passage is sufficiently large to permit of the regular interchange of gases under normal conditions. If, on the other hand, there is a complete obstruction of both passages, mouth-breathing is produced, in which the adult, although first having the feeling of inability to breath properly, soon learns to regulate his respiratory movements so that even in eating there is no difficulty in respiration; in children, on the other hand, very great dangers are present due to the possibility of their sucking milk or other foodstuffs into the larynx. Besides these mechanical effects, the nose under normal conditions acts as a filter, removing to a great extent the dust particles, bacteria, etc., in the respired air, so that, as F. Müller has shown, under normal conditions the contents of the alveoli and bronchi are sterile. In mouth-breathing, the air reaches the lungs in an unfiltered condition and at a lower temperature than under normal conditions.

As to the effect of nasal obstructions upon respiratory movements, the impediment is usually more marked in inspiration and a slower, deeper inspiratory movement is the most effective method of regulation.

Pharynx.—From the pharynx to the bifurcation of the trachea and the beginning of the bronchial system proper, we are dealing with the undivided portion of the air canal, and for that reason any obstruction even for a short period of time must prove extremely serious. In the pharynx itself, however, complete obstruction or even a marked degree of stenosis is comparatively rare. Such conditions may be met with where large pieces of food or other foreign bodies are caught in the pharynx, or in paralysis of the pharyngeal constrictors where a large mass is suddenly carried behind the velum, in the case of voluminous tumors, tonsillar swellings and retropharyngeal abscess.

Larynx and Trachea.—Stenosis of or obstruction in the larynx or trachea is of necessity far more dangerous than in any other portion of the respiratory tract because of its narrowness, especially in the region of the glottis. Among the most important conditions are those producing pressure from without, such as glandular tuberculosis, mediastinal tumors, goitre, aneurysm, etc., the impaction of foreign bodies in this portion of the tract, especially dangerous in cases of paralysis of the glottic closers, and various inflammations and swellings of the glottis itself, such as in diphtheria and œdema, various conditions of glottic spasm, such as pseudo-croup and asthma thymicum, paralysis of the glottic wideners, certain diseases, such as whooping cough, callous cicatricial contractions, which may be met with after wounds of various kinds, after operation, lupus and syphilis, and excessive granulation tissue formation, which is sometimes found after tracheotomy.

Of peculiar interest are those forms of obstruction which act as an impediment to only one phase of respiration. Thus in cases of a polyp with a long pedicle, or a flapping diphtheritic membrane situated below the glottis, we have an impediment acting only upon the expiratory phase, while an impediment to inspiration, which is far commoner, is met with in the ordinary cases of spasm of the glottis, in the cases of pediculated polyps or flapping membrane situated above the glottis, in œdema of the glottis where the swellings formed by the aryteno-epiglottidean folds lie in front of the rima during inspiration and in paralysis of the postici where the atonic cords are drawn together by the inspiratory effort. In all these cases, whatever their cause, the most serious effects are found where the impediment is situated in the glottic region, as here is the narrowest portion of the single air tube.

Obstructions in the Upper Air Tract.—The effect of all the above factors is the same in that either the entrance or the exit of the air is impeded or entirely obstructed, whether inspiration or expiration or both are effected and the degree of the obstruction depending upon the extent and location of the pathological process. Of course, if complete obstruction exists for even a few minutes, death by asphyxia takes place. If, on the other hand, the lumen shows merely a narrowing or stenosis, the amount of air is diminished according to the size of the obstacle, and such a modification of respiration takes place that the needs of

the organism are satisfied if possible; if the obstruction is of such an extent that regulation is not possible, death results from suffocation.

Obstructions to inspiration are more common than obstructions to expiration, and thus inspiratory is more common than expiratory dyspnoea. Observations in human beings have shown that the common mode of regulation in the case of obstruction to inspiration is a reduction in the number of inspirations, which at the same time become labored and deeper, due to the calling into play of the accessory inspiratory muscles, and at the same time the diaphragm, scaleni, and intercostals act more vigorously than under normal conditions. If the obstruction is very great the thorax pumps itself much emptier of air than under normal conditions, and we thus have a drawing or sinking in of all the labile portions of the thorax, such as the jugulum, epigastrium, and the lateral, supraclavicular and subclavicular regions. Obviously, the effect upon the thorax itself will be more marked in those cases in which the thorax, especially its bony portion, is peculiarly labile; for that reason thoracic deformities are much more liable to occur in early life and especially if the resisting power of the bones has been markedly diminished as in rickets.

When, on the other hand, there is an obstruction to expiration, the inspiration is normal but expiration becomes slower and labored, the elasticity of the tissues not being sufficient to bring it about, and the accessory muscles of expiration being called into play; the abdominal muscles contract vigorously, and the spinal column is bent forward in the effort to expel the air.

Thus, if the obstruction is to inspiration, we have a condition of inspiratory dyspnoea characterised by slower, prolonged and labored inspirations, the expirations being free and short, while in expiratory obstruction, inspiration is normal and expiration labored, prolonged, and strengthened. If, on the other hand, there is an obstruction to both phases of respiration, as in croup, in severe cases of oedema of the glottis, where the swelling of the aryteno-epiglottidean folds is so great that it acts as a distinct impediment to inspiration as well as to expiration, in obstruction from large foreign bodies impacted in the rima, and in the case of cicatricial contractions and compression from without of high grade, both inspiration and expiration are labored, slowed, and strengthened.

In all these cases of obstruction, if of high grade, the ordinary symptoms are varied from time to time by excessive attacks of dyspnoea, which are especially liable to be brought about by increased exertion of any kind. Also the special types of breathing, just described, may be substituted for a short time by a series of shallow, rapid respirations.

The rushing of the air through the narrowed portion of the tube produces a strident, rough, or hissing sound, the so-called stridor, the intensity of which depends upon the degree of obstruction and the strength of the respiratory movement. In all conditions where the vocal cords are no longer normally vibrated by the expiratory stream, as in inflammations, tumors, foreign bodies, destruction of portions of the cords or paralysis of the cords, hoarseness occurs, which, however,

may also be due to a paretic condition of the cords, sometimes produced by violent coughing, as in tuberculosis. An interesting type of voice, met with in conditions producing obstructions in the nasal passages or in the nasopharynx, is the so-called nasal voice, which is due to changes in the resonant properties of the oral and nasal cavities consequent upon the obstruction.

The Explanation of the Regulatory Phenomena.—It is obvious that in all these cases of obstruction, death would of necessity supervene within a shorter or longer period of time were it not for some form of increase of the respiratory activity which compensates for the disadvantages caused by the various forms of obstruction or impediment. The physiological explanation of these various types of respiratory movements has long been sought. Cohnheim showed that if an obstruction to inspiration was introduced into this portion of the respiratory tract in rabbits, the inspiration became prolonged and labored, the expiration being normal, while if the obstruction was to expiration the reverse condition took place. It has been shown that in the case of obstructions in the upper respiratory tract the change in the respiratory movements is noted before the change in the gaseous contents of the blood, and therefore we must seek for another explanation. According to the experiments of Hering and Breuer, the explanation of these regulative respiratory movements is to be found in the self-steering ability of the vagus nerve. Each expansion of the lungs inhibits inspiration and furthers expiration, while each expiration has the opposite effect. Whether this is due to chemical influences or to the effect of changes of intrapulmonary or intrathoracic pressure upon the terminal fibres of this nerve, it is impossible to state definitely.

We have thus seen that any obstacle to either phase of respiration will tend to prolong it, and that the stimuli producing such a change in respiration must come through the vagus nerves. The value of this mechanism can be easily seen if these nerves are cut, for in such cases respiration is constantly dyspnoëic. On the other hand, due to this regulatory mechanism, even more air is taken into the lungs than under normal condition, as Köhler has shown in rabbits (the reason for the increased consumption of oxygen being the increased activity of the respiratory muscles).

Obstruction Below the Bifurcation of the Bronchi.—Below the bifurcation of the bronchi there are distinctly different mechanical conditions than above this point, for in the former we have an increasing number of divisions of the air tube as we go from bifurcation to alveoli. For that reason, for any obstruction in the bronchial tree to act in the same way as an obstruction of the upper respiratory tract, all tubes of the same sectional area must be occluded to practically the same extent. Practically the only conditions which can bring about such a picture are general thickening of the bronchial tubes, general tetanic contraction of the bronchial musculature, and obstruction to each of the main bronchi synchronously. The first two of these conditions are met with in certain cases of bronchial catarrh, and much more commonly in emphysema and bronchial asthma.

If both the great bronchi are narrowed, due either to the presence of foreign bodies or to pressure from without, as by aortic aneurysm or mediastinal tumor, we have practically the same mechanical conditions as those met with in narrowing of the trachea or larynx, and the regulatory mechanism is of the same type; that is, the phase of respiration which is impeded, becomes slower, deeper, and more labored. If, on the other hand, only one of the two great bronchi is narrowed we have a distinctly different picture, and after the extremely rapid dyspnoëic type of respiration, which is inevitable when the respiratory conditions are suddenly changed, we have comparatively slight changes in the respiratory mechanism, because of the adaption to the new conditions and the fact that for ordinary demands one lung is amply sufficient. Whether we have a somewhat more rapid or a somewhat deeper type of respiration, or both, depends upon the special conditions of the individual case. In fact, the self-steering of the regulatory mechanism has for its object the attainment of the best results under the existing conditions.

Foreign Bodies.—Obstruction due to foreign bodies is most likely to occur when a deep inspiration takes place during a meal, and thus it is peculiarly liable to occur when, with the mouth full, a person yawns, sobs, sighs, or laughs. The foreign body is more likely to pass directly into a bronchus the deeper the inspiratory effort, and, due to the anatomical conditions, the right side is more likely to be affected than the left. According to the shape and consistency of the body, partial or total occlusion of the main bronchus or of one of its branches may result, while it frequently occurs, sometimes after a considerable period of time, that after a severe attack of coughing the foreign body is transferred to another bronchial branch. If the impediment is of such a nature that a slowed, more labored form of respiration will affect the lung beyond the impediment, that type is inaugurated, while if the impediment is such that practically complete occlusion takes place, the sound lung alone must perform all the respiratory functions, and increased rapidity of respiration results.

Bronchitis.—The mechanical effects of bronchitis differ markedly according to the number and size of the bronchi affected, the amount and character of the secretion, and the available respiratory forces of the patient. Thus, in catarrhal inflammation of the larger bronchi the degree of narrowing is practically never sufficient to cause a marked hindrance to respiration, while, on the other hand, in inflammation of the smallest bronchi and bronchioles the hindrance to respiration may be of extreme moment; obviously such a hindrance will be of much greater significance in children, where the air tubes are smaller and the muscular power weaker, and in the aged and feeble than in adults in a normal state of health. Thus, in bronchitis there are all grades of dyspnoea, reaching, in the case of marked obstruction in the bronchioles of a large portion of the pulmonary tissue, a degree not surpassed by any other respiratory disease.

As to the type of respiration in bronchitis, this is obviously very different according to the conditions in the individual case. Thus, if we have practically the same degree of narrowing in all bronchi of the

same caliber, there is a mechanical condition closely simulating narrowing of the trachea or larynx, and the best way of overcoming such a condition is by a slower, more forceful series of inspirations and expirations; expiration is more likely to be prolonged than in tracheal or laryngeal stenosis. In most cases of bronchitis there is simply an increased frequency of respiration. The exact cause of this is still unexplained, part of it being referable to the fever usually present, while, according to Traube, most of this quickening is referable to the stimulation by the inflammation of certain fibres of the vagus nerve. On the other hand, in certain cases of bronchitis affecting a large area where the closure of the small bronchi and bronchioles is incomplete, as for instance in a diffuse, dry bronchitis of moderately small bronchi, a considerable amount of air may reach the lungs through the affected bronchi, and for that reason the best regulation is obtained by inspirations that are deeper than normal and not too quick; in some rare cases there is even distinct slowing of the respiratory rhythm. In chronic bronchitis other conditions play a rôle; thus, we must also take into account atony of the bronchial muscles, loss of elasticity, and lack of contractile power due partly to the effect of the inflammation upon bronchial musculature and elastic fibres, and partly to the increased expiratory pressure, which is, of course, especially marked during paroxysms of coughing.

The prolongation of expiration so commonly met with in bronchitis is easily explained, being due to the fact that during expiration the contraction of the elastic thorax tends to still further contract the stenosed bronchioles, and thus render the exit of air more difficult.

Effect of Local Stenoses of the Bronchi.—These are due in the majority of cases to various forms of inflammation but occasionally to the presence of foreign bodies, and, as there is no bronchial anastomosis, the area beyond the obstruction, if complete, is lost to respiration, and therefore we have a corresponding diminution of the respiratory surface. If the stenosis or obstruction affects only a moderate proportion of the bronchi the loss is easily supported, as the respiratory surface is constituted to meet the most sudden demands for oxygen. In other cases the obstruction reaches such a grade that breathlessness occurs, and the type of respiration in such cases, the deep inspirations and the forced expirations, is in many cases sufficient to overcome or remove the obstacle.

It is interesting to consider the effect of total occlusion or stenosis upon the portion of the lungs supplied by the involved bronchi. Of course, in cases of total occlusion of a large bronchial territory the whole force of the inspiratory pull is exerted upon the pervious sections of the lungs. Experiments on rabbits show that if one main bronchus is tied, death occurs either from rupture of the other lung and pneumothorax, or because of the stasis of the blood in the abnormally dilated pulmonary vessels. If less lung tissue is cut off, however, a true compensatory hypertrophy takes place, the actual increase in growth being brought about by the increased circulation in the unaffected portion of the lungs. When a comparatively small portion of the pulmonary tissue is involved the compensatory dilatation and hypertrophy are largely confined to the contiguous portions.

Not less interesting is the effect of total occlusion of the bronchus upon the portion of the lung lying beyond it. In this, complete atelectasis occurs, the air being absorbed by the circulating blood. In the atelectatic portion of the lung the circulation continues, and we therefore may meet with products of transudation or exudation, while the small bronchi do not of necessity stop secreting, and if this secretion is abundant we may find a condition of bronchiectasis.

If, on the other hand, the bronchus is not totally occluded, but only narrowed, a different picture is presented. In cases of obstruction within the thoracic cage the expiratory efforts tend to distinctly increase this obstruction, and, in fact, in marked cases to convert an obstruction into a complete occlusion, while, as a rule, the inspiratory effort lessens the degree of the obstruction. For this reason we have a condition in which more air enters than leaves the portion of the lung lying beyond the occlusion, and thus we have dilatation of the alveoli becoming more and more marked, which may in time lead to a true emphysema, generally of the vesicular, but in extreme cases, of the interstitial type. In the vast majority it is when the smaller bronchi are affected that such a condition is likely to occur, and for that reason emphysema is met with peculiarly frequently in bronchial asthma and in *catarrhe sec.*

Bronchial Asthma.—There is no better example of a general bronchial stenosis than this. There has been much discussion as to its exact nature; the best explanation is that it is due to a tetanic contraction of the small bronchi, and that it is more a neurosis than a true inflammation. In many cases it seems to originate reflexly from various portions of the body, especially the nose.

From the hindrance to inspiration and the much greater hindrance to expiration, there is a combination of both the inspiratory and expiratory types of dyspnoea, the latter being much more marked and in its manifestations calling into play the accessory muscles of expiration. The strain upon the pulmonary tissues is so great that after a shorter or longer period bronchitis and emphysema are likely to develop. This same form of paroxysmal dyspnoea is often met with in old cases of emphysema and bronchial catarrh; in these it is certain that the condition is also due to a spasm of the bronchial musculature, set up reflexly from the inflamed mucous membrane.

Emphysema.—In this the lung tends to constantly approximate its inspiratory condition with slight excursions during inspiration and expiration, while if many septa are destroyed there is also a real loss of respiratory surface. Therefore in pure uncomplicated emphysema respiration is usually shallow and hastened, with slight disturbances during rest but marked during exertion of any kind. In many cases of emphysema, however, we have an associated bronchitis, especially a diffuse dry bronchitis of the smaller tubes, and this is likely to modify the respiratory picture; if the inflammation is such as to produce a partial stenosis of a large proportion of the bronchi we may have a diminished rate of respiration with marked prolongation of the expiratory phase. According to Sahli, the type met with may be described as prolonged expiration with expiratory stridor, characterized also by a

greater or less tendency to quickening, although we may have slowing of respiration or a normal rate.

Pneumonia.—In pneumonia the type of respiration is partly due to the diminution of respiratory surface, partly to the mechanical limitations of the lungs' excursions, partly to the commonly associated pleurisy, which renders deep excursions painful, and partly to the effect of the increased temperature and toxins upon the respiratory centre. We usually, of course, meet with a shallower, more rapid respiration, the extent of these disturbances being dependent upon the extent of consolidation, the amount of normal air space remaining, the rapidity of the process, the demands of the gaseous exchange, and the physical condition of the different parts of the compensating respiratory mechanism.

In *oedema of the lungs*, *hemorrhagic infarct*, and *pulmonary hemorrhage* the mechanical conditions are practically the same as in pneumonia, except that, as a rule, we do not see the effect of fever or toxemia.

Tumors.—We meet with a number of conditions which affect respiration, partly by pressure, partly by destruction of a certain amount of air space. Among these may be mentioned aneurysm of the aorta or of the pulmonary artery, mediastinal tumors, swollen bronchial glands, epithelioma of the œsophagus, metastatic nodules in the bronchi or lungs, mycotic foci, and tuberculous consolidations. In all these cases the character or origin of the growth is immaterial, and also whether it renders the alveoli impervious by penetration or by compression. The phenomena depend upon the amount of lung tissue thrown out of function, the degree of inhibition of free movements of the lungs, and whether the process is associated with fever and toxemia.

Bronchiectasis.—In this the dilatation must occur at the expense of a certain number of alveoli, as the thorax is a closed cavity. Thus the respiratory picture is partly dependent upon the consequent diminution of respiratory surface, partly upon the frequently associated bronchitis.

Pleural Effusion.—The question of the mechanics of pleural effusion is extremely interesting and has been the source of much discussion. According to the usual view, in the first place, the lung is compressed with a consequent diminution of respiratory surface; in the second place, we have a mechanical limitation of the lungs' excursion, while if the effusion is great we may have a compression of the sound lung as well as a limitation of its movement; in the third place, due to the lessening or lack of negative pressure, we may have less or no aspiration of venous blood, while the pressure of the exudate on the veins in the thoracic cavity may exert a marked effect upon the right heart.

Garland, who performed a very interesting series of experiments upon the mechanics of pleural effusions, differs quite markedly from most writers as to the dynamics of pleural effusion. His work is of such importance that it will be well worth while to summarize his conclusions as follows: That the letter S curve can be traced only in the upright position, and its persistence indicates the absence of adhesions in the lower part of the chest; that it is pathognomonic of a fluid effusion of the pleural cavity; that it exerts a negative pressure by virtue of its weight; that the position and shape of the lung represent the balance between

weight of fluid and elasticity of lung; that the diaphragm does not sag down until the weight of the effusion exceeds the lifting force of the lung; and that until this point is reached the heart and mediastinum are not pushed by an effusion, but are pulled by the opposing lung.

According to Rosenbach, another and more important influence is at work, which he describes as tonus. He regards the diaphragmatic displacement as third in the chain of events associated with the exudate, these being, in order, a certain dilatation of the thoracic space, due to relaxation of the muscle tonus, a secondary compensatory diminution of that portion of the lung particularly affected, and downward displacement of the diaphragm with its associated dislocation of the abdominal organs.

The conclusions of Garland seem to give a far more satisfactory explanation of the mechanics of pleural effusion than those suggested by any other writer on the subject.

Pneumothorax.—In pneumothorax the study of the mechanical conditions is as interesting as in pleural effusion. We have to consider the mechanical effects both in open pneumothorax, where there is a positive pressure in the pleural cavity, and of closed pneumothorax, where the normal negative pressure is diminished or where the pressure may even be positive, although to not so great an extent as in open pneumothorax. In closed pneumothorax when air is present and does not vary much with inspiration and expiration, respiration is not prevented, and we have practically the same conditions as those in pleural effusion. If, however, the opening is of a valve-like nature the air may possess abnormally high tension, so that finally the affected half of the thorax is expanded to a greater extent than that found even in the deepest inspiration, and in these cases the lung is not only airless but compressed. In open pneumothorax, the lung is able no longer to follow the inspiratory pull of the chest wall, little or no air enters, and atelectasis to a greater or less extent results, although, of course, if pleural adhesions are present the pneumothorax is saccular, and the atelectasis partial. Both types of pneumothorax cause, to a greater or less extent, diminution of the respiratory surface and a mechanical limitation of the lungs' excursion.

According to Rosenbach the pathogenesis of pneumothorax is not so simple as to be explainable solely on mechanical grounds; in fact, according to him, the nature of the fistulous opening, on which a special subdivision into open and closed valvular pneumothorax has been based, is of less importance than the condition of the respiratory apparatus itself. Thus, maintenance of the normal pressure relations will depend upon the size of the opening, the rigidity of the walls, the elasticity of the lung tissue in the immediate vicinity of the opening, and the irritability of the reflex apparatus.

The most complete review of the whole subject of pneumothorax including the mechanics of this condition is to be found in the monograph of Emerson.¹ To quote from this investigator, "when air is allowed to

¹ *Johns Hopkins Hospital Reports*, vol. xi.

enter the pleural cavity the lung begins to collapse. If the perforation be a parietal one and the diameter of the opening be less than that of the bronchus to that lung, the air will enter with each inspiration, and during expiration some of the lesser amount be expelled, until the lung at the end of expiration is just collapsed. Then with each succeeding breath the lung will expand somewhat with each inspiration, since more air can enter through the bronchus to fill the partial vacuum than through the perforation. With each expiration the lung will assume its former collapsed condition, since the air escapes more easily from the bronchus. The smaller the hole the greater the expansion of the lung, and in case it be then closed the lung can take no small part in respiration."

As regards the mechanics of the valvular form of pneumothorax, according to Weil the air enters during inspiration, while according to Bouveret it is the violent expiratory effort of coughing that forces air into the pleural cavity; according to Bard, coughing forces the air from the pleural cavity, and the positive tension met with in valvular pneumothorax is due to the regular play of the respiratory movements and is equal to the normal pulmonary tension.

As to the respiratory phenomena met with in pneumothorax, various investigators report slightly different observations. Gilbert and Roger found that the respiratory rhythm at the onset of pneumothorax was greatly disturbed, marked inspiratory efforts lasting for a short time; after the condition was well established in open pneumothorax, the rate becoming faster, the inspirations deeper, while in closed the rate became slower and inspiration slightly deeper, though not to the same extent as in open pneumothorax; in a closed double pneumothorax the rate increased, the amplitude diminished. According to Krebs, the excursion increased both in rapidity and depth in open pneumothorax, the increase of the rate varying directly with the diameter of the fistula, while Blumenthal found the rate increased in all forms, the volume breathed in the unit of time increased in closed and diminished in open pneumothorax, the diminution varying inversely as the diameter of the fistula, while the depth was diminished in all forms, in the open form depending upon the size of the fistula.

Other Conditions.—There are other conditions which affect the respiratory mechanism, either by diminishing the respiratory surface or by inhibiting the respiratory movements to a greater or less extent. No condition is more important in this connection than *adhesion of the two layers of the pleura*. Normally, of course, the lungs increase in volume not only in the transverse and anteroposterior diameters but also vertically; the apices and the posterior margins participate least in the change of position, while the displacement of the inferior margin of the lungs may be taken as the best measure of the expansile power of the alveoli collectively. If adhesions occur between the two layers of pleura the expansion of the lungs will be affected; the effect will, of course, be least if the adhesions are at the apex or the posterior portions of the lungs, while it will be greatest if they are along the inferior margins.

Among the other conditions which affect respiration either by

diminishing the air spaces or making the respiratory movements less free, may be mentioned large tumors within the thorax, enlargement of the heart and pericardial effusions, aneurysm of the aorta, substernal goitres, hypertrophy of the thymus, mediastinal tumors, the forcing upward of the diaphragm by abdominal tumors, ascites or meteorism, and thoracic deformities, especially kyphoscoliosis, in which that half of the thorax toward which the convexity of the spinal curve is directed may occasionally be much reduced.

Although the lung may regain its normal state when the causative factors are removed, nevertheless in a number of cases the compression is either so great or of such long duration that diminished elasticity of the pulmonary tissue results, which, of course, must act prejudicially on the expiratory contraction of the alveoli.

The Effect of the Preceding Conditions upon the Respiratory Mechanism.—The effect of these various diseases is to lessen the respiratory surface to a greater or less extent, and diminish more or less the ability of the lung to expand in regular fashion. The type of respiration met with depends not only on these two factors, but upon a number of others, among which may be mentioned whether the pathological process is local or general and its extent, whether the air spaces are entirely obliterated in the affected portions of the lungs or only partially encroached upon, whether the process is rapid or slow in development, whether or not it is associated with pyrexia or toxemia. The condition of the neuromuscular respiratory mechanism, and of the pulmonary tissues, especially as regards their elasticity, that is, the compensating help of the respiratory movements, and the demands of the gaseous exchange must be considered. We have also to consider many factors besides those definitely referable to the pathological process itself, such as the age of the patient, the functional condition of the respiratory bones and muscles, the condition of the patient's nervous system and of his various organs, notably, of course, the heart and the kidneys, his ability to have the proper amount of rest, fresh air, etc. Generally speaking, the organism accommodates itself better to a loss of respiratory surface, the slower the development of the pathological process on which this loss depends. If the loss of alveoli takes place very rapidly the respiratory symptoms are much more marked, as in the stormy symptoms met with in lobar pneumonia, acute miliary tuberculosis, pneumothorax, and acute pulmonary oedema. Generally speaking, the respiratory disturbances are greater the more the diminution of the respiratory surface, if the demand for oxygen remains the same. If fever is present there is a tendency to increased frequency, that is, a heat tachypnoea, in addition to the effects of the pathological process itself; this bringing about an increased production of carbon dioxide, and an increased pulse-rate with a consequent greater demand for oxygen.

The exact type of respiration met with in the individual condition varies very markedly, as it depends upon all the factors mentioned above. Nevertheless, in every case it is in all probability the best type of respiration to overcome the pathological conditions presented. Thus, we may have an increased rapidity of respiration, or an increased depth

of respiration, or a combination of these two, or we may meet with a shallow quickened respiration, or a slower, deepened respiration. Increased frequency of respiration is very common, especially with fever, when deep respirations cause pain, as in acute pleurisy and peritonitis, in cases where large portions of the lungs are positively prevented from expanding and where the increased rapidity is referable to an irritation of the vagus endings, as in bronchitis. In many cases of diminution of the respiratory surface a deeper respiration is frequently met with, especially when the affected air cells are not entirely obliterated. In emphysema, open pneumothorax, especially if bilateral, and in other conditions in which rapid expansion or contraction is difficult, due either to changed pressure relations in the pleural cavities, diminished elasticity of the pulmonary tissue, or impediments to either inspiration or expiration affecting a large portion of the lungs, a respiration slower than normal may be met with, and we may have either an inspiratory or expiratory dyspnoea or a combination of the two.

Generally speaking, increased rapidity of respiration with a tendency to increased depth is the respiratory type most frequently met with. Although in certain conditions, such as general pulmonary œdema and bilateral pneumothorax, death occurs unless the condition passes off rapidly, nevertheless in most of the conditions described the type of respiration inaugurated is able to compensate for the respiratory deficiency due to the pathological process itself, and the dyspnoic form of respiration is a means of compensation of the most efficient and helpful kind. Practical experience shows that by this means the functions necessary to life may be carried on satisfactorily, if not perfectly, while numerous experiments show that the gaseous exchange under the pathological conditions may be even greater than under normal conditions. Although in all cases the dyspnoic respiration is the most efficient means of compensation, nevertheless it must be remembered, in the first place, that there is a limit beyond which compensation is impossible, and, in the second place, that in all cases internal respiration is affected to a greater or less extent. In serious conditions when compensation is imperfect we can diminish as far as possible the demands for oxygen by absolute rest and by preventing anything which will act as an impediment to the compensating mechanism; thus the patients may lie upon the affected side in cases of unilateral hindrances to respiration, while in many cases the upright position renders respiration easier by facilitating the action of the auxiliary respiratory muscles, by removing or at least lessening the pressure on the diaphragm from the abdominal organs, and by facilitating the flow of blood in the cerebral veins.

The Protective Mechanism of the Lungs.—Two matters of extreme importance require mention: first, the protective mechanism of the lungs, and second, the means by which foreign bodies are removed from the air passages. The air passages may be regarded as a long, narrow, protected tube system, in various portions of which special mechanisms are introduced to prevent the entrance of foreign bodies into the deeper portions. The various mechanisms are so efficacious that, according to F. Müller, the contents of the alveoli, and of the

bronchi, even as far as the trachea, are sterile under physiological conditions. While this is mainly due to the protective mechanisms, nevertheless it is helped by the fact that in the bronchial tree the air does not move violently, diffusion being far more important than the tidal movements, so that dust and bacteria, if present, settle on the mucous membrane in a thin layer, and are then got rid of, the length, narrowness, and tortuosity of the air passages aiding greatly.

The first of these protective mechanisms is the *mucous membranes* of the nose, for on the folds and elevations, produced by the turbinate bones, a large proportion of the foreign material is deposited, as shown by the enormous increase of such bodies in the lungs when the turbinate bones are destroyed, or the nasal septum is affected. The epiglottis is in reality of less use than usually supposed, as shown by the fact that absolute paralysis of the depressors of the epiglottis, as in diphtheria and bulbar paralysis, or complete absence of the epiglottis, as met with in tuberculosis or syphilis, is without danger if the glottis is normal. In normal deglutition the root of the tongue is so placed in front of and above the entrance to the larynx that it is able to close the aperture without the aid of the epiglottis. The most important protective mechanism is the glottis, and in persons with vocal cords intact, with the glottic closers functioning properly, and with normal sensibility of the glottic mucous membrane, the danger of the passage of foreign bodies is slight. Of course, even if the protective mechanism is working satisfactorily a certain amount of finely divided particles, dust, bacteria, etc., may pass the larynx, or food may occasionally enter, but the danger under physiological conditions is minimal compared to that when pathological conditions are met with in nose, pharynx, or larynx. This danger is especially great in cases in which the glottis is affected, the entrance of foreign bodies being markedly facilitated when the vocal cords are more or less destroyed by ulceration, when the mucous membrane has lost its sensibility entirely or in part, or in paralysis or paresis of the glottic muscles. The dangers are also great in cases of tracheotomy, congenital fistula of the trachea, communications between the trachea and the œsophagus, as seen in epithelioma, between the trachea and a gangrenous focus in the lung or a suppurating bronchial lymph gland, or when an aneurysm opens into the trachea or a bronchus.

When foreign bodies have reached any portion of the respiratory tract, and when the protective mechanism has proved ineffective to a greater or less extent, there are other mechanisms by which such foreign bodies may be removed. These mechanisms are the action of the cilia and sneezing and coughing.

The most important means of removing foreign bodies from the respiratory tract are sneezing and coughing, both of which are explosive expiratory impulses set up in the main reflexly, although the latter may also be voluntarily induced. In *sneezing*, which acts as a cleanser of the upper respiratory tract, a deep inspiration is followed by an expiration so forcible that the closure of the air passages produced by the application of the soft palate to the pharyngeal walls is overcome, and the blast is forced violently through the nose, accompanied by a

loud and characteristic noise. Sneezing is usually produced reflexly by stimulation of the endings of the sensory fibres of the trigeminal nerve in the mucous membrane of the nose, although when the sensibility of these nerve endings is increased, as in a cold in the head, even cold or warm air may inaugurate the sneezing paroxysm; it also may be set up reflexly from other parts of the body.

The cleansing of the trachea and the larynx, and to a certain extent of the bronchi, although the cilia assist especially in these last regions, is mainly brought about by the act of coughing, when the foreign material is to be removed. *Coughing* consists of a deep inspiration followed by a forcible expiration, at the beginning of which the glottis is closed so that a condition of high pressure is present in the respiratory tract; when the glottis is finally opened the foreign material is forced into the mouth, the nose being shut off by the soft palate, whence it is got rid of either by expectoration or by swallowing, the act of coughing like that of sneezing being accompanied by a characteristic sound. Coughing may be inaugurated in a great many ways, but the most important is by stimulation of the sensory fibres of the superior laryngeal nerve in the mucous membrane of the larynx, although it may be set up reflexly by stimulation of any of the vagus endings of the respiratory tract. Coughing may also be set up reflexly from various other portions of the body, as from the stomach, spleen, liver, or uterus, when the feet get cold or when the body is exposed. It may be inaugurated spontaneously. In many of these cases such cough is met with only in extremely nervous people, and is probably due to an irradiation of the stimuli to the cough centre in the medulla.

A purely *nervous cough* is possible from abnormal excitability in the region of the reflex paths of the cough. In the vast majority of cases of cough due to inflammation of the respiratory tract, the surface of the mucous membrane has been pathologically changed, and this leads to a marked increase in its excitability, so that stimuli, such as the introduction of very cold or very warm air, which would not have any effect under normal conditions may produce a violent paroxysm. This increased sensitiveness explains the coughing so frequent in bronchitis before the formation of much secretion, and also in ulceration of the larynx. On the other hand the ability to cough may be markedly diminished or even absent altogether, as in diminished irritability of the mucous membrane met with in persons with anesthesia of the larynx, in comatose patients, in various conditions of deficient sensibility of the respiratory mucous membrane, as that of the bronchial mucous membrane after chronic catarrh, paralysis of the glottis, destruction of the vocal cord by ulceration, various cerebral diseases, weakness of the patient, as during tedious fevers, conditions where coughing would produce pain, such as pleurisy, peritonitis and trichinosis, and various diseases of the respiratory muscles or nerves. Whatever be the cause of this diminished ability to cough, the lung is in danger not only from the introduction of foreign bodies, but also from the retention of its own secretion; it is indispensable for the production of effective cough that the mucous membrane of the glottis, trachea, and bronchi be sensi-

tive, that the glottis be capable of closing, and that the expiratory muscles be able to overcome by their contraction the glottic closers.

While cough is usually a useful mechanism, in certain instances the violence of the paroxysm is out of all proportion to the strength of the stimulus, and in the second place, even the most powerful efforts of coughing may fail to get rid of the *materia peccans*, as when a foreign body is impacted in a bronchus, or when it is of irregular shape and has penetrated the bronchial walls. In other cases coughing may simply drive a foreign body from one bronchus into another where a new train of symptoms may be inaugurated, while in certain cases, notwithstanding the most marked respiratory efforts, the foreign bodies reach the alveoli, where they must be got rid of by other means, such as absorption or phagocytosis, since coughing cannot be initiated from the alveolar walls.

The act of coughing is by no means an entirely harmless process. In the first place it has a marked effect on the circulation, producing an increase of arterial pressure, due partly to the violent contraction of the expiratory muscles, but more to the effect of the act upon the intrathoracic pressure, there being either a diminished negative pressure, or more commonly a positive pressure; both of these conditions act as impediments to the flow of blood from the systemic veins into the heart, and thus a varicose condition of the facial veins and capillaries results, which may become permanent, while during very acute paroxysms, rupture of the capillaries, as those of the eye or of the brain, is not uncommon. Besides the effect upon the arterial, venous and capillary systems the act of coughing also affects the heart secondarily. In the second place, the act of coughing has a very marked effect on the respiratory organs themselves, for the fact that in coughing a very forcible expiration coincides with closure of the glottis means that until this closure is overcome the lungs are under a considerable degree of tension, which produces an increased pressure in the bronchi and the alveoli. This is mainly in the superior portion of the lung, since in the expiratory contraction of the diaphragm and the other expiratory muscles the lower half of the thorax is most affected, and the air is consequently driven into the upper lobe, producing, if the paroxysms are sufficiently severe or sufficiently frequent, either bronchiectasis or emphysema, or both.

As to the different kinds of cough, Sahli mentions numerous types; thus, the moist cough due to the presence of fluid secretions in the bronchi and trachea; the dry cough when no secretion is present or when its consistency is such that the cough is unable to remove it; the raw barking cough with a hoarse or aphonic voice met with in certain forms of laryngitis and due to the swollen condition of the vocal cords, although we may have it also in hysteria; the raw, but not barking, cough met with in cases of ulceration or partial destruction of the cords and due to their irregular position; the soundless cough, when the glottic closers have become weakened from ulceration, from paralysis of the glottic closers, from paresis of the expiratory muscles, or general weakness; the hollow or empty cough sometimes heard in severe cases of tuberculosis, due in some cases to diminished strength of the glottic closers and closure of the mouth, in other cases to the aërial resonance in the tuberculous

cavities; slight cough due to the irritant being slight, and usually not associated with much secretion and frequently met with in chronic catarrhal conditions of the upper air passages; and violent coughing paroxysms due to intense excitants or irritants, or due to an increased sensibility of the nervous cough apparatus.

PATHOLOGICAL CONDITIONS AFFECTING THE NEUROMUSCULAR RESPIRATORY APPARATUS

In the preceding pages it is assumed that the neuromuscular mechanism which carries out the regulatory movements is normal, but this is frequently not the cause. Although there are many variations of the respiratory movements which fall within the normal limits, such as the different modes and rates of breathing met with in children, women and men, during and after exercise or due to emotional influences, nevertheless these are of no especial moment because of the fact, as Voit and Pflüger have shown, that all such alterations have no other influence on the gases of the blood than that involved in the augmented work of the respiratory muscles. For respiration to be normal it is essential that the inspiratory muscles, which overcome the resistance of the ribs, the elasticity of the lungs and the abdominal muscles, must be in a healthy condition, while as regards quiet expiration it is essential that the elasticity of the lungs and thorax should not be impaired; in other words, the regular process of inspiration depends on the ability of the proper muscles to contract properly, while normal expiration requires the occurrence of muscular relaxation at the proper moment, when the elasticity of the lungs and of the ribs if normal effects the rest. There are numerous pathological conditions which may affect the respiratory muscles; thus the diaphragm may possess congenital or acquired defects which allow the entrance of some of the abdominal contents into the thoracic cavity, while occasionally we find a unilateral rupture of the diaphragm or the absence of one-half or the whole of this muscle.

The functional power of the diaphragm and other respiratory muscles may be impaired by various processes which bring about considerable loss of contractile power, such as severe pyrexial diseases, emphysema, chronic bronchitis and heart disease, great debility and progressive muscular atrophy, extensive cancerous infiltration, trichinosis (which mainly affects the diaphragm and the intercostals), and contiguous inflammation, such as diaphragmatic pleurisy, peritonitis and pericarditis, which affect the diaphragm partly by the extension of the inflammatory process, partly by the associated circulatory disturbances; various conditions affecting the nervous respiratory apparatus, such as paralysis of certain of the muscles, due either to a central cause, such as medullary hemorrhage, or to a peripheral cause, as in multiple neuritis, lead poisoning, etc.; conditions affecting the thoracic cage itself, such as extensive ossification of the costal cartilages, ankylosis as in arthritis deformans, and comparative immobility of the thorax, as seen especially in emphysema, where the thoracic cage tends to assume constantly the shape of forced deep inspiration; conditions in which inspiration is asso-

ciated with pain, such as recent fracture of the ribs, pleurisy, trichinosis, pericarditis, peritonitis, and appendicitis; conditions associated with an increase in the resistance to be overcome by the inspiratory muscles, such as large abdominal tumors, much abdominal fat, ascites, meteorism, tympanites, pregnancy, and pericarditis with effusion. At times one side of the mechanism is mainly affected, such as unilateral weakness or paralysis of the muscles, unilateral fixation of the thorax, and kyphoscoliosis. As regards expiration, the most important factors are those in which the elasticity of the respiratory apparatus is affected, such as the lessened elasticity of the thoracic wall and thoracic muscles, lessened elasticity of the lung tissue, met with especially in emphysema, and tonic contraction of the diaphragm; while as regards the muscles which come into play in forced expiration, they may be affected by any of the conditions mentioned as affecting the inspiratory muscles.

The immediate effect of the impediments to inspiration and expiration, as regards the gaseous contents of the blood, is that not enough oxygen enters the lungs, due mainly to the former, and not enough carbon dioxide leaves the lungs, due mainly to the latter; so that conditions arise which soon make life impossible if respiration is not modified so as to correct them. There are two means of accomplishing this: first, the reduction of oxygen consumption, which may be brought about by lessening so far as possible the amount of muscular work and by living a life as quiet as possible, and second, by increasing either the depth or the frequency of the respiratory movements. In the main these conditions act mechanically very much like a stenosis of the air passages, and may be similarly corrected, that is, if the impediment affects inspiration, the inspiratory movements become stronger, and frequently also slower, while if the expiratory portion of the apparatus is at fault active takes the place of passive expiration, and here the abdominal muscles play the most important rôle. If certain groups of muscles alone are affected, compensation may be brought about by the transference of work to the more capable muscles; thus, thoracic may be converted into abdominal breathing, and *vice versa*, while in conditions where one side alone is affected, compensation may be brought about by an increase of movement of the normal side. On the other hand, in a number of cases deeper respiratory movements either are ineffective or impossible, and in such conditions regulation is brought about by more rapid, shallower respirations; such regulation is met with when deep breathing is productive of pain, in cases when practically all the respiratory muscles are affected by the pathological process, and in cases in which there is an increased resistance to inspiration, such as emphysema and the various abdominal conditions mentioned. In many of these conditions an attempt is often made first to regulate respiration by deeper inspiration; but either the resistance cannot be overcome by this means, or the muscles are not sufficiently strong to keep up such a mode of compensation. In the case of shallow respirations there is an especially marked tendency for atelectasis, bronchial catarrh, and even pneumonia to develop because of the imperfect ventilation of certain parts of the lungs, notably the deeper portions.

The utility of regulating the respiratory mechanism so that more oxygen enters and more carbon dioxide leaves the lungs, and of regulating the oxygen demand by modifying the mode of life is easily apparent, for in those conditions the active manifestations of which pass off after a greater or less period of time, such as meteorism, typhoid fever, trichinosis, etc., life is sustained until the normal conditions have been restored, while even in those cases where complete recovery is impossible, life may not only be rendered possible, but even supportable.

ABNORMAL CONDITIONS OF THE PULMONARY CIRCULATION, OF THE BLOOD AND OF THE RESPIRED AIR

It is essential that the pulmonary circulation be unimpeded for the proper oxygenation of the blood. In a number of conditions sections of the vascular system of the lungs have been rendered impervious, as for example by thrombi or emboli in the branches of the pulmonary artery, various cirrhotic processes of the lung, tuberculous or bronchiectatic cavities, caseation of the lung, pulmonary emphysema, where many capillaries have been destroyed with the alveolar septa, compression of the lungs by intrathoracic and intra-abdominal tumors, by pleuritic effusions, in certain cases of pneumothorax, and by pericarditis with effusion. In the second place, the pulmonary circulation may be affected even when the vessels of the lungs are pervious and undiminished in number, as in various cardiac lesions, fatty degeneration of the heart, lesions of the pulmonary orifice, extreme pericardial effusion, complete adherence of the two layers of the pleura, and atelectasis and chronic bronchitis. Under any of these conditions less blood passes through the lungs, and some form of compensation is therefore necessary. This is mainly brought about by the circulatory apparatus itself, although in certain cases it is not perfect, as when the heart muscle is seriously affected, and when the derangement of circulation is absolutely too great; in such cases attempted regulation by means of a modification of the respiration is more apparent. In all cases, but especially in this latter class, there is a diminution of oxygen and an increase of carbon dioxide, and, due to the effect of the altered blood upon the respiratory centre, the respirations become deeper, which raises the partial pressure of the oxygen in the alveoli as well as quickens the circulation; the rate of respiration is sometimes slowed, sometimes quickened. As to the utility of these dyspnoëic respiratory movements, according to some observers, Filehne for instance, the form of dyspnoea in patients suffering with heart disease is absolutely useless, but this is not so, for these dyspnoëic movements further the pulmonary circulation as well as increase the partial oxygen pressure.

In anemia we have a condition in which unless some form of compensation occurs proper oxygenation is impossible, and this is so whether the condition be one of oligocythemia or oligochromemia. In such conditions the effect of the increase in the carbon dioxide and decrease in the oxygen of the blood upon the respiratory centre is to bring about

a dyspnoëic respiration (there being both a strengthening and a quickening of the respiratory movements). This mechanism tends to regulate the condition, for the exchange must be more rapid because the pulse is quicker, and the partial pressure of the oxygen in the alveoli must be increased as well. By such a mechanism the total gaseous exchange may be normal, but internal respiration is always affected. In other conditions in which the blood is abnormal, respiration is modified, as for example in uremia (in which the slowing of the respiration with prolongation of the expiratory phase is probably referable to the effects of the circulating toxins upon the respiratory centre, although many of the respiratory symptoms met with in this condition are referable to the associated myocarditis, bronchitis, or pulmonary œdema).

The characteristic effect of hyperpyrexia upon the respiration is an increased frequency, the so-called heat tachypnoëa.

The variation in composition of the respired air also plays a most important part, as the penetration of gases through the epithelial cells of the lung is mainly dependent on the partial pressure of the alveolar air. The effect of diminution of air pressure is well known, the degree of intensity of the symptoms depending upon the extent of the diminution and upon the special susceptibility of the individual and the condition of his respiratory, circulatory, and hematopoietic systems. It is well recognized that the majority of men are capable of enduring a diminution of air pressure to 450 to 400 mm. of Hg. without discomfort, and in some cases even one-half an atmosphere. As regards the effect of the diminution of air pressure on the exchange of gases, Fränkel, Geppert, and Loewy have shown that there is no change in the gaseous exchange if the pressure is one-half an atmosphere or more, while if it is less than this there is an increase in the carbon dioxide production, and also a slight increase in the oxygen intake, due to the increase of the respiratory movements. As to the regulatory mechanism in these cases, a superficial, more rapid type is usually met with, due partly to the ascent of the diaphragm produced by the expansion of the intestinal gases, while if the pressure sinks still further, deeper respirations appear. As to increased density of the air, Loewy has shown that even twice an atmosphere has no appreciable influence upon the respiratory mechanism.

As regards the effect of carbon monoxide on the respiratory mechanism, if it is present in the air to a greater extent than 0.8 to 1 per 1000, carbon-monoxide hemoglobin is formed, which affects the organism partly by lessening the amount of oxyhemoglobin, partly by the effect of the carbon monoxide upon the nerve endings. The mechanical effects of carbon monoxide poisoning are exactly the same as those produced by slow bleeding or by gradual diminution of the respiratory surface.

CERTAIN ADDITIONAL QUESTIONS IN THE MECHANICS OF THE RESPIRATORY DISEASES

Dyspnoëa.—It must be remembered that dyspnoëa is essentially a form of regulation designed to counteract the existing impediment or

pathological condition, while the extent of the dyspnoea depends upon the degree of oxygen deficiency. Of course, by rest and regulation of the mode of life it is possible to diminish the consumption of oxygen, but this and the elimination of carbon dioxide cannot be reduced below a certain minimal amount, while it is a practical impossibility to spare for any considerable length of time all muscles except those absolutely necessary. The term dyspnoea is used in a double sense, first to signify increase in the rate or in the depth of the respirations, or labored and slow respirations (in other words, objective dyspnoea), and second, the sensation of air hunger (subjective dyspnoea). Due to the regulatory mechanism the patient may have the former without the latter, while in certain conditions, notably hysteria and melancholia, he may have the latter without the former. In some cases subjective dyspnoea is not present, as in many patients at rest suffering from kyphosis, chronic bronchial catarrh, extensive pleural adhesions, moderate emphysema, and small tuberculous foci, although objective dyspnoea is present.

Subjective dyspnoea is almost always present in extreme grades of emphysema, advanced tuberculous lesions, extensive acute pneumonia, stenosis of the trachea, and pneumothorax. Although persons with impaired respiration instinctively limit the expenditure of oxygen, and although in slighter impediments to respirations, even though the oxygen saturation of the blood is below normal, a certain equilibrium is established in the organs and tissues, nevertheless, if conditions supervene which demand a larger amount of oxygen, such as exertion or fever, or in which the equilibrium between the blood and the organs is not maintained, we meet with definite signs of the imperfection of the respiratory mechanism, partly in the form of subjective dyspnoea and partly in the form of cyanosis. As Sahli says, the presence of marked objective dyspnoea without cyanosis is a clinical proof of the view that the intensity of the respiratory movements is not entirely dependent upon the grade of the aëration of the blood, but is influenced directly by hindrances to respiration. Thus, under all conditions objective dyspnoea seems to diminish cyanosis and the feeling of subjective dyspnoea, but in all severe hindrances to respiration, especially when the neuromuscular respiratory mechanism is not normal, cyanosis will be present sometimes to a considerable degree, although even in these conditions the organism may finally accommodate itself to the impoverished blood, and the organs may perform their functions comparatively well, and with this there is, as a rule, less and less subjective dyspnoea.

Changes in the Respiratory Centre; Cheyne-Stokes Breathing.—There are a number of conditions in which the respiratory centre is pathologically affected, and of these none is more interesting than the so-called Cheyne-Stokes respiration. Among the conditions in which it is seen are various severe affections of the brain, such as tumors and hemorrhage; various cardiovascular affections; various diseases of the respiratory apparatus, especially those associated with unconsciousness, and chronic nephritis. It has also been noted in healthy children, or even adults, especially during sleep. Associated with this peculiar form of respiration, characterized by inspirations of gradually increasing depth, reaching

a maximum and then diminishing and followed by a pause, sometimes lasting as much as forty-five seconds, are other associated phenomena; thus, during the respiratory pause there is often a marked slowing of the pulse, a distinct narrowing of the pupils, while marked symptoms of air-hunger are often met with during the phase of increasing inspiratory efforts. There are various explanations of this condition, although all agree that it has much to do with the reduction of irritability of the respiratory centre due to long-continued impairment of the arterial circulation in the medulla.

That form known as Biot's respiration, which is especially frequent in meningitis but is also seen in other brain diseases and severe general diseases, characterized by respiratory pauses lasting from several seconds to one-half a minute or more, repeated more or less periodically, is also unquestionably due to changes in the respiratory centre. The extremely deep respirations met with in various poisonings and intoxications, as uremia, diabetes, and hydrocyanic acid poisoning, are in all probability due to the effect of the poison upon the respiratory centre.

Eyster has studied Cheyne-Stokes breathing by means of the Erlanger sphygmomanometer. He found two groups of cases, first, those with a rise of blood pressure and an increase of pulse-rate during the period of dyspnoea, with a fall during the period of apnoea, and second, those with a fall during dyspnoea and a rise during apnoea. In the latter class were the cases associated with cardiac and arterial disease, while of the former class Eyster had two cases, one of cerebral hemorrhage, the other with a history of intense headache and left-sided clonic spasm with a choked disk in the left eye. Eyster found that in the first group, that is, cases associated with increased intracranial tension, the underlying condition of periodic respiration is an alternate anemia and period of blood supply of the brain and medulla, the former being associated with apnoea, and occurring when the blood pressure is below the line of intracranial pressure, while the period of respiratory activity is associated with the period of blood supply to the brain, and occurs with the rise of the blood pressure above that of the intracranial pressure. The reason that these changes in blood supply should cause the opposite effect upon the respiratory centre to those observed is that the irritability of this centre is periodically much reduced or even lost when the blood pressure is below the line of intracranial pressure. Eyster was unable to give a satisfactory explanation in the second group of cases.

Mode of Death in Respiratory Diseases; Asphyxia and Slow Suffocation.—While in many cases the dyspnoic respiration is the means of saving life, and while in all cases life is prolonged thereby, nevertheless there are many conditions in which the external respiratory disturbances are greater than can be compensated by the modified respiratory movements, and thus suffocation occurs, the clinical picture being markedly different according to whether the condition is suddenly or gradually produced. In human pathology we do not often meet with cases of death by acute asphyxia; it is seen, however, in certain conditions, such as complete and sudden occlusion of the pulmonary artery, fatal spasm of the glottis, constriction of the trachea, large hemorrhage filling up

all the bronchi, sudden paralysis of the respiratory muscles, sudden bending of the trachea in patients with goitre, and those rare cases of unilateral pneumothorax suddenly complicated by pneumothorax of the other side. On the other hand, slow suffocation is the cause of death in a large number of respiratory conditions, as in glottic or pulmonary œdema, laryngeal diphtheria, pneumonia, bronchitis, pleural effusion, trichinosis, emphysema, and pulmonary tuberculosis, in which for days, weeks, or months the respiratory disturbances have been present. The mechanical conditions which may lead to slow suffocation are many, the impediments to respiration may gradually increase, finally reaching such a point that the strongest dyspnoëic respiration is incapable of correcting the condition.

The picture in acute asphyxia or sudden suffocation is an extremely striking one, characterized by the most violent, stormy, and deep respirations, with dilated nostrils, wide-open mouth, stretched-out neck, the head back, and all the accessory respiratory muscles as well as many other muscles actively involved. The vasomotor centre is strongly excited, and we have a contraction of the splanchnic vessels, a dilatation of the cutaneous vessels, and an increase in the arterial pressure, while the heart is slowed from the strong vagus stimulation, all of these factors helping to bring the maximum amount of blood to the brain. The patient shows marked restlessness, and then convulsions of gradually increasing intensity, leading to a condition of complete insensibility or paralysis, with a few feeble respiratory efforts separated by long pauses, and finally death, with a diminution of the arterial tension during the final stage, and a tendency of the cardiac contractions to persist after respiration has ceased.

Slow suffocation is not a striking picture, and is not marked by the stormy phenomena so characteristic of acute asphyxia. There is usually a complete absence of the strikingly irritative phenomena, there is no marked increase of dyspnoëa, no convulsion, and no evidence of irritation of the vasomotor and vagus centres. The pulse is usually small, the body movements feeble and languid, the temperature often low, the skin cool. The picture is one of a gradual narcosis of the various centres, and all the functions become less and less active. There is no especial complaint of air-hunger, nor is the picture one of striking objective dyspnoëa, the accessory muscles being often not used at all; the respirations become frequent and shallow, gradually becoming weaker.

In certain conditions we have a state half-way between that of acute asphyxia and slow suffocation, and the picture presented bears a resemblance to each of the two; thus, the irritative phenomena of acute asphyxia are seen to a certain extent, but the narcotic phenomena of slow suffocation modify their manifestations.

CHAPTER XXIII

DISEASES OF THE NASOPHARYNX, PHARYNX, AND TONSILS

By FRANCIS R. PACKARD, M.D.

ACUTE NASOPHARYNGITIS

Etiology.—Acute inflammations limited strictly to the nasopharyngeal region are of rather rare occurrence. When they do occur they are usually exacerbations of a chronic inflammatory condition. The mucous membrane of the nasopharynx being continuous with that lining the nose is almost always more or less involved in inflammations of the Schneiderian membrane, and frequently after the rhinitis has disappeared the nasopharyngitis which has been associated with it remains. Occurring primarily, acute nasopharyngitis is generally the result of exposure to cold or damp. It is very apt to follow sudden changes in temperature. It is occasionally seen in connection with digestive disturbances. It sometimes arises from the inhalation of irritant vapors or dust. It is apt to occur in conjunction with or following acute infectious diseases, such as scarlet fever and diphtheria.

Pathology.—The manifestations are those of acute catarrhal inflammation of the mucous membrane. There is the usual stage of acute engorgement of the bloodvessels, followed by increased glandular activity with profuse secretion. The inflammation either subsides by the ordinary processes of resolution, or may assume a chronic form.

Symptoms.—The patient's first complaint is generally of a sensation of discomfort in the back of the throat. At first there is a dry cough; after some days the secretion, which is at first clear and white, becomes thick and mucopurulent and may be quite profuse. The attack is apt to be attended with slight fever, the temperature rising to 101° F. Occasionally the patient will complain of tinnitus and a sensation of fulness in the ears owing to occlusion of the pharyngeal extremities of the Eustachian tubes.

Treatment.—Nothing affords more comfort than douching the nasopharyngeal space with warm normal salt solution, or with a warm alkaline antiseptic solution. This may be accomplished either by allowing the patient to snuff up the solution through the nares, or by the physician injecting the solution into the nasopharynx by means of a postnasal syringe. Should the patient complain of much sore throat and pain, it is comforting for him to inhale hot medicated vapors. For this purpose nothing is more satisfactory than the compound tincture of benzoin. After cleansing the nasopharynx, great lessening of the

congestion will be produced if a strong solution of nitrate of silver be applied on a cotton pledget directly to the mucous membrane. The nasal passages should be kept open in order that respiration may be free, and for this the local application of adrenalin solution (1 to 5000) is useful. This should be followed by the use of a bland oil spray containing a little camphor and menthol.

CHRONIC NASOPHARYNGITIS (POSTNASAL CATARRH)

Etiology.—Chronic nasopharyngitis may be the result of repeated attacks of acute nasopharyngitis. More usually, however, frequent acute attacks of nasopharyngitis are the manifestations of an underlying chronic inflammatory condition. Chronic nasopharyngitis is very commonly associated with gastro-intestinal disturbances. It is a frequent sequel of acute infectious diseases, especially influenza, scarlet fever, and diphtheria. The abuse of alcohol is a common cause, chiefly because of the digestive disturbances engendered by it. Chronic nasopharyngitis frequently results from, or, if it exists, is kept up by the use of tobacco. Intranasal deformities, or chronic obstructive conditions within the nose, often cause the pharyngeal mucous membrane to become inflamed, and the condition continues until the cause is removed. Of the direct causes of chronic nasopharyngitis, the most common is exposure to a damp climate in which the patient is subject to sudden variations of temperature. Thus it is especially prevalent near the Atlantic seaboard of the eastern United States. Occupation is frequently not only a predisposing but also an exciting cause when it exposes the patient to the inhalation of irritant vapors or dust.

Symptoms.—The most characteristic symptom is the sense of irritation which is almost constantly present in the nasopharynx, causing the patient to have a tendency to hawk, in an effort at relief. This only serves to irritate the inflamed structures yet further. Frequently the patient's throat becomes so sensitive and the irritation so great, that retching or even vomiting results. The patient complains of continuous postnasal dropping of mucus. There is, as a rule, not very much secretion to expectorate, such as there is being thick, tenacious, and slimy. In advanced cases the discharge is apt to be muco-purulent and greenish, and occasionally we see the formation of crusts and scales, which are apt to be somewhat blood-stained because of abrasion of the mucous membrane. The secretion in the postnasal space frequently undergoes decomposition and renders the breath offensive. The voice is generally husky and without the proper resonance. There are very apt to be aural disturbances, sometimes of quite marked severity, because of obstruction of the pharyngeal orifice of the Eustachian tube, occasionally from the extension of the inflammation up the tube, and at times because of the nasopharyngeal secretion entering the tube. The mucous membrane of the pharynx or larynx may show catarrhal changes. Disturbances of digestion are very common with chronic nasopharyngitis, generally taking the form of dyspepsia. On examination the nasopharynx

will be seen to contain a quantity of thick stringy secretion, upon the removal of which the mucous membrane will present a dry, glazed, and congested appearance. Sometimes there is considerable swelling so that it is hard to inspect the upper portions of the postnasal space.

Treatment.—Of all the measures, none are more efficacious than those which deal with general hygiene. The clothing should be regulated in order that the patient's bodily temperature may be kept as even as possible. For this purpose he should wear, both winter and summer, some form of mesh underwear. Undergarments of this character permit free evaporation of the perspiration and do more to further the activity of the skin and to prevent chilling of the surface than anything else. Thick flannel undergarments should be avoided, as they induce perspiration and prevent evaporation. If the patient is able to stand a cold tub bath every morning it will greatly promote the circulatory activity of the skin. If he cannot take the plunge or shower bath, he may at any rate douche his neck, shoulders, and chest with cold water. Careful instruction should be given as to the proper ventilation of his bed-room, as these patients are very apt to form an idea that "taking cold" is promoted by night air, and hence they exclude it. If the patient leads too sedentary a life, some regular form of exercise should be insisted upon. Dietetic errors should be corrected, and the use of tobacco and alcohol regulated, or, if necessary, interdicted.

The patient should be given an alkaline antiseptic douche, with directions to snuff it up through the nostrils into the nasopharynx, following which he should be directed to use a bland oil spray. Locally there are many substances which prove of value, their usefulness varying greatly in different cases. At least two or three times a week, at the commencement of treatment, the physician should himself thoroughly cleanse the nasopharynx, and apply some astringent or alterative preparation to the inflamed mucous membrane according to the indications present. For thorough cleansing it will generally be found necessary not only to use a solution through the anterior nares, but also to wash out the nasopharynx with some form of postnasal syringe. Any of the ordinary alkaline antiseptic solutions may be used, such as Dobell's solution, or those which are made up as the various so-called antiseptic nasal tablets. Should the secretion in the nasopharynx be offensive, a weak potassium permanganate solution used as a douche will often give gratifying results. After the muco-pus which has collected in the postnasal space has been removed, nitrate of silver in a solution of 30 to 60 grains to the ounce may be applied with cotton on an applicator, and will prove more generally useful than any other application. In mild cases, glycerole of tannin will frequently prove of value. Should there be a very granular condition of the mucous membrane, it is well to try the application of some caustic, such as lactic acid in a strength of 1 dram to the ounce. If the physician uses a strong caustic, great care should be taken that the neighboring healthy tissues are not touched. For this purpose the application should be made only with a good reflected light. If there is a quantity of granulation tissue requiring thorough extirpation, its destruction by means of the electric cautery is sometimes necessary.

This is a very delicate procedure and should only be performed by one who is accustomed to the performance of delicate manipulations within the throat. If the cautery is misapplied the cicatricial contractions which follow may be of the most serious character.

**HYPERTROPHY OF THE LYMPHOID TISSUES IN THE NASOPHARYNX. ADENOID GROWTHS IN THE NASOPHARYNX.
HYPERTROPHY OF THE PHARYNGEAL TONSIL**

This condition is really an hypertrophy of the glandular tissue which normally exists to a greater or lesser extent in the vault of the pharynx, in other words, of the tissue which is generally known as the "pharyngeal tonsil." The term "third tonsil" is frequently applied to these adenoid vegetations. The etiology is obscure. It undoubtedly occurs most commonly in conjunction with enlargement of the faucial tonsils, and is accordingly spoken of as one of the manifestations of the lymphatic diathesis. Although it occurs with marked frequency in children who suffer from tuberculous or syphilitic taint, it is, nevertheless, seen in the children of healthy parents, and it would seem more rational to consider its presence in children who had inherited tuberculosis or syphilis, as a result of the anemia attendant upon those conditions rather than as a manifestation of the inherited disease.

Climatic conditions undoubtedly exercise an influence; thus the condition is much more frequent in low, damp localities in which there are frequent changes of temperature than it is in better climates. Hypertrophy of the pharyngeal tonsil occurs so frequently in certain families that there is no doubt that an hereditary factor is present in many of the cases. It is doubtful if the condition is ever congenital, although a condition of nasal catarrh is often noticeable in young infants in whom there is a subsequent development of adenoid vegetations in the nasopharynx. Kyle holds that the cause of the so-called inherited tendency to adenoids is frequently found in the inherited family nose, the hypertrophy of the glands in the nasopharynx being more common in children whose nostrils have a narrow slit-like orifice than in those whose nostrils are wide open. In both children and adults this glandular hypertrophy is frequently found in association with hypertrophic rhinitis.

Pathology.—Adenoid vegetations in the nasopharynx are generally composed of a mass of hypertrophied lymphoid glandular tissue, covered with epithelium. Farther down in the structure, there are ramifying trabeculae of connective tissue with lymphoid cells lying between them. The proportion of lymphoid to connective tissue varies greatly in different specimens, thus, in very young children who have not been subject to repeated inflammatory attacks or congestion of the tissue, the structure is soft and the glandular lymphoid element predominates. In older patients the vegetations have usually been the site of various local congestive and inflammatory changes which have resulted in the deposit of inflammatory material with overgrowth of connective tissue and consequent hardening of the structure. The surface of these growths is generally very markedly lobulated or mammillated.

Symptoms.—The most prominent symptoms are those which arise from nasal obstruction, and of these the most striking is the appearance of the face which results from habitual mouth breathing. Everyone is familiar with the aspect of the unfortunate beings who are unable to respire properly through the nose. The dull, expressionless face, lacklustre eyes, wide-open mouth, with protruding upper lip and hanging lower jaw, accompanied by an inability to fix the mind upon a task, and the general stupidity and mental dullness frequently lead to their being regarded as mentally deficient. In fact, it is this mental sluggishness to which Guye, of Amsterdam, gave the term "aproxesia." There is also often an associated deficiency of hearing, the result of obstruction of the pharyngeal orifices of the Eustachian tubes. This deafness adds materially to the child's apparent stupidity. These children are rendered more unattractive by the fact that they are generally irritable and cross because of their constant physical discomfort.

The obstruction to nasal respiration is almost invariably most marked at night when the circulation is more sluggish, and mucus more apt to accumulate. This results in restless and disturbed sleep, and frequently in nightmares whereby the child is deprived of natural refreshing slumber, and the discomfort is materially aggravated. Quite often the patient is brought to the physician because of restlessness at night, and for the snoring and grunting which are so noticeable at that time. As a result of the air not being moistened and warmed by its passage through the nasal chambers, patients who suffer from adenoids are also frequently subject to inflammations of the pharynx and larynx, or even to attacks of bronchitis. In this way adenoids are probably the most common exciting cause of asthma and spasmodic croup in young children. The child's voice is affected at a very early stage and in a very characteristic manner. The loss of nasal resonance causes the voice to lose its natural resonance. There is generally considerable mucous discharge from the nose, and a lack of ability to properly expel this causes the child to keep up a continuous sniffing.

Of all the evil results which adenoids may produce, there are none more serious than those which occur in the ear. The aural complications vary greatly as regards their manifestations and their seriousness. There may be attacks of pain due to interference with the patency of the Eustachian tube on the affected side. This same obstruction, however, frequently leads to serious results in the middle ear, the result of constant interference with its proper ventilation through the Eustachian tube, giving rise to chronic catarrhal otitis media, and leading to impairment of the hearing. More serious is the constant liability to infection of the middle ear. The vegetations are always swarming with microorganisms, and there is no doubt that their proximity to the Eustachian tube frequently permits of their access to the middle ear.

Children with adenoids are often subjected to repeated attacks of inflammation of the fauces, pharynx and faucial tonsils, particularly when the latter are hypertrophied. As a result of these, there is apt to be enlargement of the lymph glands about the lower jaws and cervical region. The presence of adenoid growths in the nasopharynx is also

frequently responsible for the maintenance of a chronic catarrhal conjunctivitis. Peculiarities in the formation of the hard palate, and various irregularities of the teeth are also in many instances to be attributed to the interference with nasal respiration.

Diagnosis.—This generally gives but little difficulty. The peculiar facial expression and the history suffice in many instances to make the condition plain. Examination by posterior rhinoscopy is frequently a difficult matter in children, but enough can usually be seen with a mirror to justify the diagnosis, if the vegetations are present. Examination through the nares with a speculum and probe is sometimes more easily accomplished, and is of great value should it be impossible to make a satisfactory postnasal examination. A digital examination is usually possible, although, as it is terrifying and sometimes painful, it is to be avoided unless deemed absolutely necessary.

Treatment.—This consists solely in the removal of the adenoid mass, the only questions being as to the suitable time, the method to be used, and the anesthetic to be employed. Although their presence in sufficient amount to produce serious symptoms always demands their removal, nevertheless, the demand is not so urgent as to interfere with the surgeon delaying the operation until the patient shall be in the best condition for it. The general health is apt to be considerably below par, and it is well to give a little time to building up before the operation is performed. It should not be done while there is any acute inflammatory condition in the air passages or ears, as the existing condition will almost invariably be aggravated. The removal of adenoids is preferably done with the patient under the influence of a general anesthetic. For this purpose ether is to be preferred. The child should be placed in a supine position with the head hanging over the operating table in such a manner that the blood will tend to flow out through the mouth instead of down into the larynx, or a modified Trendelenburg position may be used. The mass may be removed with a Gottstein curette, or one of its numerous modifications, or with the forceps designed by Lowenberg. Should hypertrophy of the faucial tonsils be associated, the latter should be removed while the patient is under the anesthetic and just before the removal of the adenoids is undertaken.

DISEASES OF THE PHARYNX

The pharynx possesses the unique distinction of forming a portion not only of the upper air passages but also of the digestive tract. This renders its mucous membrane very susceptible to influences and conditions which affect that of the digestive tract. Thus, disorders of digestion and assimilation are very apt to be accompanied by pathological changes in the pharynx. The expression "stomach cough" is not, in many instances, an improper one to apply to the cough which accompanies a congestion of the pharynx due to digestive derangement. The continuity of the pharyngeal mucous membrane with that of the rest of the respiratory tract leads to its frequent involvement in conditions

affecting the integrity of the latter. Any obstruction to nasal respiration is apt to be productive of serious inflammatory changes in the pharyngeal mucous membrane. Such nasal obstruction causes the inspired air to pass directly into the pharynx without having been warmed and moistened by previous passage through the nostrils. Consequently, from the air taking up its moisture, the surface becomes dry, congested, and predisposed to inflammatory changes. It is this factor fully as much as its continuity of structure that causes the pharyngeal mucous membrane to share, as a general rule, in any inflammatory disorder of the nose or nasopharynx.

ACUTE PHARYNGITIS

Etiology.—This occurs but rarely as an exclusive entity. It generally coincides with an acute digestive disorder or is an exacerbation of a chronic inflammation of the pharyngeal mucous membrane. Owing to its very exposed position, it is remarkable that the pharynx is not more frequently the site of pathological changes. The commonest cause is exposure to wet or cold, or rapid changes of atmospheric temperature. It also occurs in conjunction with acute digestive disorders. Excessive smoking frequently excites an attack.

Symptoms.—The symptoms are not, as a rule, very marked or severe. There is a “raspy” feeling or soreness, sometimes true pain, in the pharyngeal region, occasionally extending up along the Eustachian tubes. Swallowing is usually painful, and there is more or less cough, accompanied by a small amount of thick mucopurulent expectoration. The attack may be ushered in by chilly sensations, and slight malaise and mild fever usually attend it, as do also occasionally general pains and constipation. On inspection, the pharyngeal mucous membrane is seen to be red and somewhat swollen. At first the surface is dry and glazed, but as soon as secretion is established there is much more discharge. Frequently there is marked prominence of the small bloodvessels on its surface. There is almost always also considerable redness of the fauces and tonsils.

Treatment.—In almost every instance it is better to begin this by free purgation. This is particularly beneficial if we use calomel in divided doses followed by a saline. The salicylates exert an almost specific influence in most attacks. If the patient’s stomach is upset, or during the period when calomel is being given, it is better to let him take five grains of salol every two hours in lieu of the more powerful (but at the same time more irritant) salts of salicylic acid. Locally, great relief will be experienced from the use of various lozenges or gargles. If the mucous membrane is very dry and glazed, a lozenge of chlorate of potash is often most useful. If there is reason to associate the attack with the gouty diathesis, guaiacum lozenges should be tried. If the pain is intense cocaine lozenges will often afford relief. A lozenge containing camphor and menthol is also useful in allaying the severe irritation. Sucking cracked ice lessens the congestion and gives great comfort.

Although gargles are not as efficient as direct applications to the parts, nevertheless, a bland antiseptic gargle, such as Dobell's or normal salt solution, is often very grateful. If the congestion of the mucous membrane is very marked, it is well to paint the surface with a strong solution of nitrate of silver (30 to 60 gr. to the ounce, 2 to 4 gm. to 30 cc.). A very strong solution of silver nitrate not only acts as an astringent but is an antiseptic, and to a certain extent an analgesic. The patient should be confined to one room, if not to bed. He should be placed on a light diet, and forbidden to smoke or use alcohol. He should likewise use his voice as little as possible.

CHRONIC CATARRHAL PHARYNGITIS

Etiology.—This very frequent affection is particularly apt to occur in those whose occupation requires constant use of the voice, hence it is frequently termed "voice user's" or "clergyman's sore throat." In such persons it occurs usually as the result of straining the voice, particularly by using it in a faulty manner or at times when there is some inflammation of the parts concerned. Other local factors are the use of tobacco, and the inhalation of irritant substances such as the fumes of acids or alkalis, and other gases. Chronic pharyngitis frequently results from catarrhal affections of the nose, most generally because of nasal obstruction causing mouth breathing. When there is considerable dropping of mucus in the back of the throat from nasopharyngitis, the pharyngeal mucous membrane becomes inflamed and irritated not only from the direct action of the secretion, but because the efforts to expel the mucus cause congestion of the entire pharyngeal wall.

Chronic pharyngitis is frequently seen in association with chronic diseases of the liver, kidney, and heart, as a result of passive congestion. It is one of the commonest manifestations of chronic alcoholism.

Pathology.—In the early stages there is a general hyperemia. Later, the membrane becomes thickened, and there is marked increase in the connective-tissue elements, with the formation of prominent granulations upon the surface. The increase in the connective-tissue elements extends to the submucous tissues. The process, as a rule, does not markedly involve the glands in the mucous membrane. In many instances the engorgement of the bloodvessels is the most prominent feature.

Symptoms.—The chief subjective symptom is a cough which is irritable, unproductive, and easily excited by change in atmosphere. The mucous membrane of the throat is red and congested, with considerable dry, slimy mucus adherent to its surface. The voice is generally quite markedly changed, there being considerable huskiness and the patient may at times lose the voice almost completely. A curious complaint is of a frequent desire to swallow; occasionally swallowing is accompanied by pain. There is engorgement of some of the bloodvessels.

Treatment.—This should first be devoted to the underlying cause. If this is found to be a faulty use of the voice, the patient should be given instruction to correct this. The closest attention should be paid

to the condition of the digestive tract. Even if the pharyngitis is not dependent upon a disordered digestion, the latter is apt to be associated with it, and its correction is an important factor. The habits, as regards tobacco and alcohol, should be carefully noted. Locally, an alkaline antiseptic wash, such as Dobell's solution, should be prescribed to be used as a spray. For cleansing purposes it will be found much more efficacious if the upper portion of the throat be sprayed out through the nostrils in addition to the direct spraying of the pharyngeal mucous membrane. Frequently, gargling with warm salt solution will be found more agreeable and more useful than the use of solutions through the atomizer. The local application of a strong solution of nitrate of silver (gr. 30 to 60 to the ounce) daily, or every other day, is a useful adjuvant.

CHRONIC FOLLICULAR PHARYNGITIS

This is characterized, as contrasted with the preceding, by the marked involvement of the glandular elements in the pharyngeal mucous membrane. This produces a granular appearance which has caused the term "granular pharyngitis" to be used interchangeably with the term "follicular." Its etiology is, in most instances, similar to that of chronic catarrhal pharyngitis. Following attacks of acute infectious diseases, such as scarlet fever and diphtheria, a chronic follicular inflammation of the pharyngeal mucous membrane is quite frequently left.

Symptoms.—The subjective symptoms are usually much more noticeable than in a simple chronic catarrhal pharyngitis. There is generally more cough and the voice is much hoarser. The cough is unproductive, except for occasional sticky masses, which are dislodged with difficulty. The pain, which is apt to be a particularly disagreeable feature, is of an aching character, and sometimes very sharp. Upon examination, the posterior pharyngeal wall is seen to be dry and glazed, and of a reddish color; scattered across its surface are numerous prominent granulations. There is usually a scanty amount of mucus present upon it.

Treatment.—This must be directed especially toward the correction of any underlying diathesis or constitutional cause. The hygiene of the patient's daily life must be carefully inquired into, particularly as to his habits regarding alcohol and tobacco. If he is a voice user, he should have instructions as to the proper method for its employment. The stimulation of the glandular elements of the mucous membrane to increased activity will be found of greatest advantage. This can be done best by the administration of the iodides internally, and by the local use of stimulating solutions of iodine. These can be advantageously employed in solutions of increasing strength, accompanied by potassium iodide, in glycerin as a medium. Another remedy of service is potassium chlorate, in the form of lozenges, to be dissolved in the mouth at frequent intervals. The patient should use a gargle consisting of hot salt solution, or of some alkaline antiseptic solution at frequent intervals.

RETROPHARYNGEAL ABSCESS

Etiology.—Suppuration in the retropharyngeal tissues is of very common occurrence in young, healthy children. It occurs but rarely in adults, and, in the few adult cases reported, the infection has been traceable to a pus focus in the immediate neighborhood of the pharynx, such as spinal abscess, or a carious tooth. In children, retropharyngeal abscess frequently follows diphtheria, scarlet fever, and measles.

Symptoms.—The onset is insidious, frequently three to six days elapsing before the attention of the physician is directed especially to the throat. For some days before localizing symptoms present themselves, the child will be obviously ill, as shown by fever, general malaise, and loss of appetite. The first symptom directing attention to the throat is generally pain on swallowing. Very shortly the voice becomes muffled, dyspnoea is soon marked and a dry cough begins. Upon examination a smooth rounded swelling can be detected occupying the postpharyngeal wall and extending downward toward the larynx. In some cases the swelling is seen on the lateral walls of the pharynx, and it is in these instances that the pus burrows downward to the greatest extent. Obstruction to respiration may cause marked cyanosis. The condition is not, as a rule, accompanied by any very marked rise of temperature, generally not above 101° F. In adults, the most prominent symptom is dysphagia, the dyspnoea being not nearly so marked.

Treatment.—By the time a retropharyngeal abscess has made itself evident as such, the pus has generally pointed to such an extent that its evacuation by incision is urgently indicated. This can readily be accomplished without a general anesthetic if the parts are well cocaineized. Should pointing not have occurred, it is well to make several incisions into the swollen tissues, as this relieves the pain and frequently prevents further accumulation of pus. Applications of ice to the neck externally will generally afford relief to the pain. If an early incision is not made the pus is apt to burrow, as a rule, in a downward direction, and very serious results have been reported. Death has occurred from hemorrhage from the carotid or other arteries, and from œdema of the larynx.

LUDWIG'S ANGINA. ANGINA LUDOVICI OR ACUTE PHLEGMONOUS PHARYNGITIS

This is not frequent, although a number of isolated cases have been reported. It is essentially a deep-seated diffuse suppuration of the submucous pharyngeal tissues, and is due to streptococcus infection.

Symptoms.—The attack, as a rule, begins with a chill which is soon followed by intense pain in the throat, difficulty in speaking and swallowing, and sometimes marked dyspnoea. The temperature becomes elevated, sometimes to 104° to 105° F., and the pulse correspondingly rapid. Examination reveals an intense congestion and swelling of the pharynx, generally bilateral and extending downward, frequently

involving the epiglottis and adjacent tissues. The throat externally is swollen; the tissues feel hard and tense to the touch.

Treatment.—The disease is characterized by great physical prostration, so that free stimulation is indicated from the onset. Locally, cold should be applied. The swollen pharyngeal tissues should be freely opened wherever a purulent focus can be located. In some of the reported cases, tracheotomy was necessary.

ANGIONEUROTIC ŒDEMA OF THE PHARYNX

This peculiar affection has in recent years been brought prominently to the notice of the profession by the comparatively large number of cases reported. T. H. Halsted¹ reported a number of cases and appended a very full bibliography. The diagnosis at times presents considerable difficulty. The affection occurs in connection with digestive disturbances, usually in persons of neurotic tendencies. It is frequently seen in association or alternating with attacks of urticaria. As a general rule, the appearance of wheals on the pharynx is accompanied by the appearance of similar lesions on other parts of the mucous membrane of the upper air passages. Death from rapidly occurring œdema of the larynx has been reported. The symptoms are a feeling of fulness and pain in the throat. On examination, clear, pellucid swellings are seen, varying from the size of a small pea to a cherry, distinctly circumscribed, and without any associated congestion of the mucous membrane. The wheals may remain for some days, or disappear within a few hours.

Treatment.—The effects of local treatment are but slight. We should direct our efforts to finding what lies at fault in the digestive or eliminating systems. Alkalis administered in large doses have seemed to be of service, and the salicylates have been used. There seems to be in some instances a tendency to spontaneous subsidence of the trouble, cases having been studied in which there was no recurrence after a duration extending over some years.

DISEASES OF THE TONSILS

The faucial tonsils are really a large pair of lymphatic glands, the functions of which are but imperfectly understood. As with other lymph glands, they probably protect the organism from infections of various kinds by acting as filters, and by in some way lessening the toxicity of microorganisms which come within their sphere of activity. Although they are beneficent in their activity, the tonsils are very subject to morbid changes. Thus, they frequently become hypertrophied to such an extent as to interfere seriously with normal respiration, and they undoubtedly, under many circumstances, instead of acting as protectors against the invasion of microorganisms, serve rather as portals of entry.

¹ *Transactions of the American Laryngological Association*, 1905.

The bacterial flora of the tonsillar surface is surprising in its number and variety and many virulent bacteria are found in the crypts.

Morbid changes in the tonsils play a most active part in the etiology of rheumatic fever and of the endocarditis and chorea which are seen so frequently in association. The tonsils as part of the lymphatic system are subject to involvement in the various disorders of it; thus, hypertrophy of the tonsils is most frequently seen accompanying the condition known as the "lymphatic diathesis." There are several factors which render the faucial tonsils especially susceptible to inflammation. Their location subjects them to constant exposure to the inspired air and contact with food or other things which may be taken into the mouth, and their irregular surfaces with wide open cryptic orifices make it an easy matter to understand the frequency with which they become the site of local infections

ACUTE TONSILLITIS

Practically every acute inflammation of the tonsils involves both the parenchyma and the follicles of the gland. It is therefore better to consider acute tonsillitis under one head rather than attempt to divide the disease into the parenchymatous and follicular varieties.

Etiology.—The chief predisposing cause lies in hypertrophic enlargement of the glands. The exciting cause of the attack is usually found in exposure to cold or damp.

Pathology.—There is congestion of the tonsil with much epithelial proliferation especially manifested in the lining of the follicles. The desquamated epithelial cells, mixed with the fibrinous inflammatory exudate, accumulate within the follicles and appear upon the surface of the swollen tonsils as white patches. Cultures from these white masses show many bacteria, especially staphylococci and streptococci.

Symptoms.—The attack may involve one or both tonsils. It is accompanied by much pain in the throat. This is usually constant in character, and increased by efforts of talking or eating. It frequently extends up toward the Eustachian tube on the affected side. The patient generally experiences great difficulty in phonation. Occasionally the tonsil becomes so swollen as to seriously interfere with the swallowing; there is not apt to be any interference with respiration. Accompanying these local symptoms, the patient usually complains of headache and backache. The attack, as a rule, is ushered in by a chill, or at least by chilly sensations; the temperature soon becomes elevated, generally, however, not much higher than 102° or 103° F. The tongue is usually coated and the bowels constipated, and there is almost always marked malaise frequently out of proportion to the objective symptoms.

The cervical glands on the affected side generally become somewhat swollen. Opening the mouth is very painful, sometimes so much so as to give great difficulty in the proper examination of the throat. When we examine the throat, one or both tonsils will appear swollen, with patches of grayish-white or white exudate filling the crypts. There is also, practically always, more or less redness of the surrounding tissues.

Diagnosis.—As a rule, this presents no especial difficulty. The most serious error is to confuse it with diphtheria. In diphtheria, the exudation which is seen upon the face of the tonsil is of the nature of a membrane, which is closely adherent to the underlying surface. Upon attempting to wipe it off, it will be found very firmly attached, and, if wiped off, the underlying surface will bleed; the false membrane is also, as a rule, tinged with blood. The exudate in diphtheria is apt to be found on neighboring structures as well as upon the tonsils; thus, it frequently involves the uvula and the pharynx. A bacteriological examination is to be relied upon for final decision.

Prognosis.—An acute tonsillitis usually subsides in three or four days if promptly and properly treated, but the patient may be left in a very weak and depressed condition. There are practically no sequelæ, except that frequent attacks seem to increase any hypertrophy of the tonsil already present.

Treatment.—The constitutional management is of as much importance as the local treatment. It is wise to give a mercurial purge followed by a laxative salt. In acute tonsillitis the salicylates will be found to exert an almost specific action. The earlier their administration the more efficient is their action, and they should be pushed to the therapeutic limit. Should there be much fever, one of the coal-tar antipyretics may be combined. Locally, the crypts of the tonsils should be cleansed of the deposits in them by peroxide of hydrogen applied in full strength with a cotton swab. After the application the throat should be sprayed out with an alkaline wash, and a solution of nitrate of silver (1 to 8) applied to the inflamed area. This should be done daily, and in the interval the patient should be instructed to gargle his throat every two hours with peroxide of hydrogen diluted about one-half its full strength. Frequently great benefit may be derived from lozenges containing guaiacum, chlorate of potash, or benzoate of sodium. The patient will derive much comfort from sucking cracked ice, which not only lessens the pain but also the congestion. Externally, cold applied to the throat is grateful.

PERITONSILLAR ABSCESS OR QUINSY

The term “quinsy” should be confined to suppuration of the peritonsillar tissues and not applied to the occurrence of pus within the structure of the tonsil itself. In most cases there is more or less involvement of the tonsil in the inflammatory process, but in many instances the tonsil is not invaded at all. Quinsy is most frequently seen in persons with large or ragged tonsils, the wide-open cryptic orifices apparently affording a convenient portal for the entrance of the infective microorganism.

Pathology.—Although the pus from a peritonsillar abscess contains many varieties of staphylococci and streptococci, a specific microorganism has not been isolated. The abscess generally forms in the loose cellular tissues immediately surrounding the tonsils, and burrows in various directions, especially into the tissues of the soft palate and downward into those of the pharynx. The loose arrangement of the tissues in this

neighborhood facilitates the spreading of the pus. For this reason, and because of pus naturally following the dependent direction, the abscess usually points downward toward the larynx. Although quinsy most frequently occurs on but one side, bilateral cases are quite often seen.

Symptoms.—The onset is usually marked by a chill followed by a rapid rise of temperature (103° to 105° F.). From the beginning the patient complains of intense pain in the throat, a pain that is gnawing and throbbing, much aggravated by attempts at eating and talking, and usually extending up in the direction of the ear on the involved side. With this the patient complains of headache; the tongue is furred and the bowels constipated. Articulation is much interfered with, the patient talking as though his mouth were full. There is almost always great prostration.

Diagnosis.—This, as a general rule, presents but little difficulty. Examination reveals the peculiar location and nature of the swelling, and palpation readily elicits fluctuation when pus has once formed. Duke reports a case in which a colleague opened an aneurysm, mistaking it for a quinsy. This would hardly seem possible with the absence of inflammatory symptoms and if the peculiar pulsation was taken into account. From the sore throats which are associated with the acute exanthemata, the diagnosis should be readily made, considering the location and character of the swelling and the absence of membrane. Tumors or new growths of the tonsils have been confused with it, but in such conditions the acute inflammatory symptoms are wanting.

Prognosis.—Although, as a rule, favorable as regards life, cases with a fatal result have been reported. This generally occurs because of the rupture of the abscess into the air passages, with death by asphyxia, although several cases have been reported in which death occurred from hemorrhage, the result of erosion of a bloodvessel. Each attack is apt to be followed by recurrences, probably because of some local condition favoring infection.

Treatment.—The salicylates should be given as soon as the attack is recognized, and their use continued until the patient is thoroughly under their influence. Their action is greatly aided if they are given in conjunction with an alkali, such as sodium bicarbonate. Alkalis have also locally a beneficial action, and, if the patient is instructed to use an alkaline gargle or take a little sodium bicarbonate into his throat at frequent intervals, it will be found very serviceable. Another remedy, of service internally, is guaiacum. A teaspoonful of the ammoniated tincture of guaiacum given in milk every four hours in many instances certainly seems to modify the attack. It is also used in the form of lozenges. The bowels should be opened by the administration of a mercurial, followed by salts.

Locally, the pain is much relieved by the patient sucking cracked ice. He should also be given a spray or gargle of diluted hydrogen peroxide. This is especially useful after the abscess has been opened, as it burrows into the tissues and gets at the pus in a way nothing else can. The use of cocaine locally to relieve pain is inadvisable, as its constricting effect upon the bloodvessels is followed by a reaction which renders the pain

if anything worse than before it was applied. Externally, cold applied by means of a coil to the neck will be found very grateful. As soon as pointing occurs, the abscess should be opened. As a general thing the incision should be made a little below the point where the uvula and soft palate merge, and it should be done under good illumination, the tongue being kept out of the way by a tongue depressor and the parts having been previously cocaineized. The incision should be directed downward and inward toward the median line, in order to avoid opening the large vessels in the neighborhood of the tonsil. After the pus is once evacuated the quinsy generally clears up very rapidly. After the attack is over, the patient should have his throat examined and any ragged or diseased tissue should be removed in order that the dangers of reinfection may be lessened.

CHRONIC INFLAMMATION OF THE FAUCIAL TONSILS

The real functional importance of the tonsils is so little understood that the question of their pathology is obscure. In early life, under normal conditions, they present the ordinary structure of a pair of lymphatic glands. Although their overgrowth or hypertrophy may cause serious interference with respiration, the most important condition which demands their treatment or ablation is when they become the source of infection, either local or general, or when alterations in their structure render them subject to repeated attacks of inflammation with various sequelæ, such as peritonsillar abscess, infection of the lymph glands of the neck, or suppuration of the middle ear. The association of pathological conditions of the tonsils with rheumatic fever, arthritis and endocarditis is proved beyond doubt. They are undoubtedly the chief portals of infection in tuberculosis of the cervical lymphatics.

Pathology.—As a rule, both tonsils are found diseased, but occasionally the condition is unilateral. Simple hypertrophy is frequent in children, and if the tonsil is not otherwise diseased shows a tendency to disappear at puberty. The pathological changes which lead to the development of the so-called “cryptic” tonsils are not clearly understood. The orifices of the tonsil crypts, which are normally closed, present as openings in which accumulations of caseous material containing numerous bacteria are found. This is frequently attributed to repeated attacks of acute follicular tonsillitis. On the other hand, acute follicular tonsillitis is one of the chief manifestations of chronic disease of the tonsils.

Symptoms.—Chronic enlargement of the tonsils may exist for many years without giving rise to any notable disturbance either local or general, but usually the patient exhibits at least some degree of the expression characteristic of the habitual mouth breather. Consequent upon mouth breathing is the development of a condition of irritability of the fauces and pharynx, producing a dry, irritative cough. In children sleep is apt to be restless and disturbed, and, especially if the enlargement of the tonsils is accompanied by the presence of adenoid vegetations in the nasopharynx, nightmare is not infrequent. The voice lacks nasal

resonance. If the follicles of the tonsils contain caseous material, the breath is generally offensive. These accumulations, acting very much like foreign bodies, are often the cause of an irritative, non-productive cough, the source of which may be overlooked. The patient with chronic disease of the tonsils is subject to repeated attacks of acute tonsillitis, with its sequelæ. The liability to contract diphtheria or scarlet fever is undoubtedly increased by the presence of hypertrophied tonsils.

Treatment.—Although many alterative or astringent applications have been extolled with a view to bringing about a reduction of the size of hypertrophied or diseased tonsils, it is doubtful if any of these possess any real value. Iodine is the most useful and is generally used in combination with potassium iodide in glycerin. Glycerol of tannin, nitrate of silver, and sulphate of zinc are rarely used now. Of certain caustics, such as chromic and nitric acid, which were once in vogue, and the use of the cautery too much cannot be said in reprobation.

If the tonsils are the site of chronic disease, the best treatment is their complete ablation by surgical measures. The guillotine has fallen into disfavor, as it is difficult to remove all of the tonsil with it, and the same is true of the various operations with the tonsil punch. Most laryngologists after dissecting the tonsil from its attachments and drawing the gland from its bed with a tenaculum, complete the removal with some form of wire snare. The operation is one which requires good technique. It should, whenever possible, be performed in a hospital and under general anesthesia. That the operation is too frequently lightly regarded is a fact to be deplored. These patients manifest a tendency to take a general anesthetic badly; the hemorrhage is frequently considerable, and there is great danger of infection and sepsis both during the operation and for some days after it. The danger of operating on hemophiliac patients is a very real and present one. In every large hospital service great numbers of children are sent in by the school inspectors for the removal of their tonsils. In many instances there is no reliable previous history available. In the only instance in which the author had the experience of operating upon a patient with hemophilia, the hemorrhage was controlled by the injection of 20 cc. of rabbit serum, after the child had been having continuous oozing for four or five days, and every other means had been tried without avail. Cases of death from what was considered as status lymphaticus have been reported. The children who are subjected to the operation are so often strumous, cachectic, or badly nourished that they constitute a peculiarly unfavorable class. In view of the above circumstances the present trend of opinion is decidedly adverse to the removal of the tonsils by ill-trained operators, and strongly in favor of regarding such operations as hospital procedures to be performed with every possible precaution and careful technique.

MYCOSIS OF THE TONSILS AND FAUCES

This is characterized by the presence over the surface of the fauces and tonsils, and in the crypts of the latter, of white masses of granular material and epithelial debris, almost invariably accompanied by the presence of the *Leptothrix buccalis*. In many instances microscopic examination reveals the presence of keratoid material, and many authorities go so far as to consider the process as a keratosis of the epithelium. Others have attributed the condition to the activities of the leptothrix. It is probable that the presence of the latter is more than a coincidence, although it can hardly be regarded as a causal factor, because it occurs in the buccal secretions of almost all persons, whereas the pathological condition of mycosis is one of considerable rarity. There is undoubtedly a marked proliferation of the epithelium underlying the masses, and the latter have an organic relation to the epithelial surface. It would seem that mycotic tonsillitis should be regarded as a proliferative disorder of the epithelial covering of the fauces and tonsils, and that the lesion is frequently of the nature of a keratosis.

The condition occurs in young and otherwise healthy adults; it is very much more common in the female sex. The reason for discrepancy in the sexes is not far to seek, as mycotic tonsillitis is practically never seen in those who use tobacco.

Symptoms.—Definite symptoms are rare. It is usually accidentally discovered during an inspection of the fauces. Occasionally patients complain of slight sticking sensations, especially noticeable during efforts at swallowing, but even this minor discomfort is, as a rule, not complained of by the patient until his attention has been directed to the condition of his throat. Upon inspection the whitish or yellowish-white masses, varying from the size of a pin head to that of a small pea, are readily seen projecting from the surface of the mucous membrane. The spots vary in number, sometimes only one or two can be found, at other times as many as fifteen or twenty. They may extend down on the posterior wall of the pharynx, and a favorite locality for them is in the glosso-epiglottic space, and about the root of the tongue. The masses stick firmly to the surface, and can be removed only with difficulty, generally leaving a small bleeding spot. Mycosis is unaccompanied by any general manifestations, although its recurrence in association with digestive disorders has given rise to the supposition that there was some relation between them.

Diagnosis.—This presents but little difficulty. Occasionally the masses are mistaken for the accumulations which occur in follicular tonsillitis, and there are cases on record in which a mistaken diagnosis of diphtheria was made. Both of these should be readily excluded by careful examination, and, in case of doubt, a microscopic examination of a portion of one patch makes the diagnosis certain.

Treatment.—The fact that this disease occurs only in non-smokers would suggest that the cultivation of the habit of using tobacco would be an easy solution of the difficulty of treatment. However, in cases

in non-smoking men the development of the tobacco habit has not always been efficacious in curing the complaint. So far as local treatment is concerned, the results are unsatisfactory. It is of great importance to attend to the proper hygiene of the mouth and teeth. The patches should be cleansed away as far as possible by frequent application of hydrogen peroxide, nitrate of silver or iodine. In many instances the application of a strong solution of bichloride of mercury is of service.

Much can be done by the removal of the masses by diligent scraping with a sharp curette before the applications of the various solutions. Should all minor measures prove ineffectual, it is frequently possible to effect a cure by the application of chromic acid or trichloroacetic acid, or by the use of the galvano-cautery. In many instances the condition continues in spite of all measures and finally spontaneously disappears.

TONSILLOLITHS

The formation of calculi within the tonsils is not very frequent, although it is quite common to find calcareous masses in the caseous material which accumulates so often within the crypts. Tonsil stones are generally the result of calcareous degeneration of the tonsillar secretion which has accumulated in the follicles. They usually give rise to but little disturbance, although the patient may complain of a feeling of fulness in the region of the tonsil in which the stone is located. Their recognition is, as a general rule, easy, although quite frequently they are so deeply situated within the structure of the tonsil that they are only discovered accidentally in the course of a tonsillectomy. The treatment consists in the removal of the calculus by the use of a pair of forceps, accompanied if necessary by the dissection of any tissue which may interfere with its extraction.

CHAPTER XXIV

HAY FEVER

By W. P. DUNBAR, M.D.

Introduction.—John Bostock, a London physician, in the year 1819, described a complaint which attacks certain persons every year, lasts six to eight weeks, and manifests itself as a catarrh of the ocular conjunctiva as well as of the nasal and pharyngeal mucous membranes, beginning with tickling, and burning. Some patients also have asthmatic symptoms.

Hay fever is to be considered as a product of modern culture. Working people or members of uncivilized nations are very rarely attacked by it. Hay fever especially attacks individuals who belong to the higher strata of culture, and particularly those who are exposed to intense intellectual strain or excitement. Exact statistics as to the extent of the disease do not exist and must be hard to collect. It can, however, be stated that hay fever has proportionally its greatest distribution in North America and next among the English and Germans. In Germany, England, and North America the disease usually begins toward the end of May, and lasts everywhere from five to eight weeks; in America the disease reappears annually in August and only exceptionally in the same persons who had been attacked in the spring.

Etiology.—Concerning the *cause*, very divergent opinions have arisen. From the beginning all authors were in agreement on one thing, namely, that the etiological researches would have to consider two important factors: First, that only those persons are affected with hay fever who show a *special individual predisposition* to the disease, as otherwise it could not be explained why the same persons are attacked each year. Secondly, a *definite exciting agent* must exist, which causes a paroxysm in these predisposed individuals. Without such a supposition it would be inexplicable that the disease should begin yearly in each predisposed person at a fixed time.

Bostock, and many others after him, believed that the disease is based on a hypersensitiveness of the mucous membranes to *dust, bright light, heat, or special odors*. They explained away the fact that such noxious influences are operative throughout the year, while the disease is associated with a particular season, by assuming that the activity of these substances was suddenly increased by the first heat of summer. Such a conception does not take into consideration that in the United States hay fever appears at a time when the heat of summer is already on the wane. The *pollen theory* was generally accepted as correct after Blackley had established that the time of onset coincided with the time when the

first gramineous pollen is in the air, and that the manifestations are most intense when the amount of pollen in the air is the greatest.

Several considerations against the pollen theory were urged. Helmholtz maintained that hay fever is caused by *bacteria*. He found many adherents, and for a time the bacteria theory might be considered predominant. When the author began to occupy himself in 1895 with the etiology of hay fever, the study of the then modern literature forced him to believe that hay fever actually was produced by bacteria. The results of his own first researches strengthened this attitude, for during the attack definite bacteria were found on the mucous membranes of hay-fever patients, almost in pure culture, which did not exist in the same persons before or after. All attempts to reproduce attacks with the pure cultures of bacteria isolated were as unsuccessful as those of other experimenters. That bacteria obtained in almost pure culture from hay-fever patients did not produce attacks of hay fever would not in itself have induced the writer to abandon the bacteria theory, for in other investigations it was also proved that bacteria can in one day completely lose and never thereafter recover an originally intense toxicity. But a puzzling fact was the observation that paroxysms of hay fever appeared suddenly and intensely, and then inside of a few hours or even less completely disappeared. The worst attacks of hay fever occur on railroad journeys. The writer proved, however, that a person can ride on railroads on even very hot days during the hay-fever season through blossoming meadows and rye-fields, so long as the windows and doors of the compartment are closed tight and a handkerchief is held in front of the face; on the other hand, as soon as the windows are opened, severe attacks are induced. From these observations it seemed that the agent must be present in great numbers everywhere in blooming meadows and rye-fields. Finally, the writer proved that even in hay-fever season one can keep free from attacks for weeks by not going out-of-doors and keeping the doors and windows carefully closed.

In 1902 the writer observed a thick cloud of dust over fields of blossoming rye, and found that it was formed of rye pollen. That suggested the investigation directly of blooming grasses and stalks of rye. The author was of the opinion that one could arrive at safe conclusions in reference to the cause of hay fever *only if it were possible to separate this agent completely from foreign admixtures, especially from bacteria, and if one could produce all the symptoms of hay fever by this agent, independent of temperature and weather conditions, and especially without regard to any particular season, and if finally the proof could be elicited that the agent acts only on those persons who are subject to hay fever, and produces absolutely no symptoms in other persons.*

By means of the pollen of grass blossoms it was possible to produce all the symptoms of hay fever in hay-fever patients. The same material was completely inactive toward normal persons. Pure pollen caused attacks of hay fever, but when the experiments were tried somewhat later with the same material on the same patients after the hay-fever season they resulted negatively. Woodward seemed, therefore, to have been right in his conclusion that grass pollen is absolutely harmless

outside of the hay-fever season. However, when the experiment was repeated after the membrane of the pollen had been destroyed by treatment in a mortar, it was possible to produce paroxysms in a very short time. With normal persons the ground pollen was inactive. Even in winter the experiment succeeded with all hay-fever patients who submitted to it, while with normal persons every symptom was lacking.

Since the assertion is continually made that hay fever is an imaginary disease and that attacks are brought on in especially sensitive persons merely by looking at a picture of blooming fields, the attempt was made to rule out subjective influences by giving the patient alternately active and inactive material. By these means it was observed that some normal individuals experienced a tingling if merely a drop of distilled water or of normal salt solution were placed on their conjunctivæ. In such instances, however, all objective manifestations were always lacking. Apart from such occurrences, the investigations allowed of only one interpretation, and their correctness was soon confirmed by many observers in England as well as in the United States. After establishing these facts, experiments were instituted to find out how the various symptoms, especially the asthma, arise, and whether the hay-fever poison resides in any particular component of the pollen grains.

The next question to be decided was whether a *supersensitiveness of the mucous membranes* is at the bottom of hay fever. It was an open question as to whether the pollen grains irritated simply mechanically as foreign bodies. Investigations by the applications of dust, soot, and other foreign bodies showed that hay-fever patients are no more sensitive to such things than normal persons. Besides, it could be proved that the pollen of certain plants whose surface is all covered with fine prickles does not irritate hay-fever patients, while the surface of pollen which caused paroxysms is absolutely smooth. Accordingly, the theory that a purely mechanical irritant was the cause of the attacks had to be abandoned.

Various authors have asserted that certain *odoriferous bodies, ethereal oils*, or similar substances produce hay fever. The pollen of the limes and roses studied by the writer proved to be totally innocuous to hay-fever patients. But grass blossoms do not smell. It is claimed that sweet vernal grass, *Anthoxanthum odoratum* particularly, must be considered as the cause of hay fever. But the pollen of this grass has no odor. If grass pollen is extracted with alcohol and ether, one succeeds in getting ethereal oils which strongly irritate the mucous membranes not only of hay-fever patients, but also of normal persons. They are, however, not felt, because they are present in the pollen in too small amount to be noticed under natural conditions.

By salting out the crushed grass pollen the writer succeeded in separating the active substance entirely, so that the residue even in large amounts was inactive to hay-fever patients. But from the extract the active principle could be precipitated quantitatively by means of alcohol. The precipitate showed all the reactions of albumin and proved to be active to hay-fever patients in the smallest amounts. In some cases $\frac{1}{40000}$ mg. was sufficient to produce strong objective signs. Normal

persons can be subjected to large amounts without any reaction whatever. It was difficult to accept the view that a well-characterized albumin represented the poison of hay fever. It appeared too startling that a chemically pure albumin, perfectly indifferent in its action to most persons, should be for certain individuals such an extraordinarily active poison. It seemed possible that an *enzyme action* might enter into the question. In pollen there are various enzymes, but by chance it was ascertained that grass pollen can completely lose its toxicity without the slightest damage to its enzymes. The recent researches of Kammann on the albumin of grass pollen show that the *pollen globulins* are totally inactive, and that the toxin is attached to the albumin. Pollen toxin is, therefore, a *toxalbumin*. It is absolutely unaltered by heating to 56° C.; at 70° to 80° C. it loses one-quarter of its strength; at 90° to 100° C., three-quarters; at 120° C. it is still active, and is completely destroyed only at 150° C.

With the establishment of the fact that the poison of hay fever is a toxalbumin we had arrived as far in the characterization of the poison as the status of chemical knowledge at that time permitted. Further experiments were naturally easier and more delicate through the possession of the pure toxalbumin, especially in regard to the dosage of the poison. To the objection that one should not work with the isolated poison, but employ fresh pollen extracts in these investigations, it may be stated that the writer considered the work with crushed pollen only as a makeshift until the active principle was isolated.

One chief objection to the pollen theory has been raised in the fact that comparatively little pollen has been found in examinations of air. By the toxin solution obtained it was possible to show that the amount of poison contained in one or perhaps a few rye-pollen grains suffices to produce manifestations of severe irritation in hay-fever patients. During the hay-fever season we were able to find grass pollen everywhere in the air in very large amounts. Liefmann in Halle, just as Blackley previously in London, found the most pollen in the air on the days that hay-fever patients suffered most. Sometimes as many as 4,000,000 grass-pollen grains settled within twenty-four hours on one square meter of surface. In Halle, Liefmann was able to show that he inhaled about 500 pollen grains inside of twelve minutes, *i. e.*, with each inspiration 2 or 3 pollen grains. Some hay-fever patients could not exist were they to take up such an amount of pollen, if nature did not come to their aid by eliminating a large amount of poison through the mucous secretions before it is dissolved. The observation that individual hay-fever patients suffer before the exact hay-fever time and before the general blooming of grasses was also used as an argument against the pollen theory. Liefmann cleared up this point by proving that as early as April a few grass-pollen grains are found in the air in regions where the general blooming does not appear until several weeks later. In an analogous manner we can explain the appearance of delayed attacks of hay fever by proof of the presence of pollen in the air long after the general blooming period. The fact that hay-fever patients suffer less on *rainy days* has its natural explanation in the demonstration that pollen is completely

precipitated by rain. At the same time the rain causes a lively formation of pollen in the blossoms, which explains the fact that in a few hours after the cessation of the rain the pollen is soon conveyed in larger amounts to the air. It thus happens that patients even a short time after rain suffer from severe attacks when near blooming grasses. On hot, dry, windy days the paroxysms are most severe and grass pollen is present in the air in greatest amount.

In the United States the blossoming of grasses occurs at the same time as in Germany. There they are accustomed to call hay fever also *June cold*, *rose fever*, or *peach catarrh*. In the United States during the first half of August the same manifestations of the disease reappear, but in the main not in those persons who suffered in the spring. The number of those in the United States who suffer in the autumn seems to be much larger than in the spring. Only a few suffer from both forms.

North American Autumnal Catarrh.—After concluding the above experiments it seemed probable that American autumnal catarrh also was caused by plant pollen, but probably from another race of plants. Suspicion had already fallen on *goldenrod* (*Solidago*) and *ragweed* (*Ambrosia*), which are everywhere present in the United States as weeds, but are absent in European countries. A ragweed plant was studied which had been taken care of in an herbarium for eleven years. With the pollen of this plant the writer produced typical manifestations of hay fever in such patients as suffered with American hay fever. Further study confirmed the view that ragweed above all else is practically the cause of American autumnal catarrh, and goldenrod to a less extent, because goldenrod does not scatter pollen through the air in such amounts as does ragweed. Active toxalbumin was procured from the pollen of both plants. Finally, it was proved that the pollen of *chrysanthemums* and of all kinds of *asters* has a very poisonous action on patients who suffer from American hay fever, but not on those who suffer only from the spring catarrh.

In connection with the investigations already described we have examined altogether 169 kinds of plants with reference to the activity of their pollen. For spring hay-fever sufferers the pollen of all *Gramineæ* and *Cyperaceæ* that were examined (respectively 25 and 8) were found to be toxic. For autumnal catarrh sufferers the pollen of 11 kinds of plants was found to be toxic, among which are 5 *Ambrosiaceæ* (ragweed) and 2 of the *Solidago* (goldenrod) family.

Toxin.—The symptoms produced by the hay-fever toxin vary with the site of application. After instillation into the conjunctival sac one observes itching, tears, photophobia, conjunctivitis with pericorneal injection, up to chemosis. When stronger doses are used a part generally passes through the *ductus nasolacrimalis* into the corresponding nasal cavity and there produces signs of irritation. After nasal applications, sneezing, marked mucous secretion, reddening and swelling of the nose appear; after aspiration of the toxin, severe coughing with expiratory dyspnoea and stridor; after rubbing on the skin, intense itching, local erythema, and wheals.

We have also made *subcutaneous injections* of the pollen toxin. If

a small amount of the toxin were injected subcutaneously in the forearm, the first manifestations appeared in ten minutes, and consisted of severe sneezing, with plentiful secretion from the nasal mucous membranes and considerable swelling of both nostrils; after thirty minutes a dry cough appeared, with a slight, tenacious expectoration, and at the same time the face swelled and became very red and cyanotic. A marked injection of the conjunctivæ developed and later chemosis. In both ears there was a feeling of tension; objectively, however, no change could be perceived in the tympanic membranes. One hour after the injection, tormenting asthmatic disorders with audible stridor arose; an hour later an urticarial-like eruption of large wheals appeared over the whole skin, associated with violent itching; three hours after the injection the forearm began to swell. The œdema spread during the following night to the whole arm. The œdema of the arm and a turgid appearance of the face remained for several days. All other objective phenomena disappeared by the next morning. The temperature remained normal from the beginning. For a week after the experiment the patient experienced a disturbing sensation of weakness and exhaustion, as well as occasional attacks of palpitation of the heart.

From the above studies we were able to obtain a comprehensive view as to the origin of so-called *hay asthma*. This can arise at times after the entrance of the poison into the circulation, and can then be considered a reliable indication of the resorption of the poison. On the other hand, we have also been able to show that the aspiration of the poison can under certain conditions produce asthma. A hay-fever patient who had never suffered from hay asthma suffered repeatedly from asthma after handling the extremely finely powdered pollen toxin.

In the meanwhile the pollen toxin has been tried outside of Germany, in the most scattered countries, France, England, Russia, United States, India, Sumatra, and Australia. Everywhere hay-fever patients reacted to the *gramineæ* toxin and at the same time normal persons were unaffected by it. On the basis of this demonstration the writer adopted the view that by means of the pollen toxin the often difficult *diagnosis* of hay fever could be easily and surely made.

Spring hay fever appears to represent, from an etiological point of view, the same disease throughout the world. But, on the other hand, all patients who suffer from North American autumnal catarrh react to *ragweed* and *goldenrod pollen toxin*, and are almost without exception insensitive to *gramineæ* toxin. According to this, American autumnal catarrh represents etiologically a disease entity which differs from spring hay fever, but the two diseases stand in close relationship. Whether other forms of hay fever exist cannot with certainty be determined at present. In the cases observed where such a suspicion arose, the question could be decided in the negative. In patients who cannot stand the odor of cats or horses a specific susceptibility to pollen toxin has been shown repeatedly. In Colorado, according to local conceptions, a form of hay fever can be produced by the third blossoming of *alfalfa* (*Medicago sativa*, Lucerne). It has, however, been shown that the affected patients react to ragweed and goldenrod toxin and not to

gramineæ toxin. In China a catarrh exists which is attributed to the privet blossoms (*Ligustrum vulgare*). It has been proved that privet pollen contains a toxin which has identically the same action as gramineæ toxin. These statements tend to show that to the present no support has been found for the conception of the existence of a third form of hay fever.

Antitoxin. The blood serum of animals which gave a strong reaction to pollen toxin showed neutralizing properties to the toxin. With a few animals this appeared after a few injections, with others only after regular treatment for months. The antitoxic power of the animal's serum increased in proportion to the immunity to the poison, and obtained a very considerable value after several years' regular continuance of the injections. The standardization of this antitoxin, unlike other antitoxins, cannot be made on animals, but only on hay-fever patients. A solution of the pollen toxin which is sufficient to cause a severe irritation of the mucous membranes of hay-fever patients is mixed with different amounts of the serum to be tested. The mixtures stand an hour at 37° C., then it is determined which of them no longer produces inflammation when instilled on the conjunctivæ of hay-fever patients. If, for instance, the serum in a 30-fold dilution neutralizes this toxin solution, it is given the value of 30 units. During the first year we succeeded in obtaining sera of 20 to 30 units. Now nearly all the horses furnish almost constantly sera of 40 units, the oldest horses even reaching 60 units. If the test solution of toxin is used in sufficient strength we can by our titration method arrive at concordant results even with hay-fever patients of very varying susceptibilities.

By this titration method we have also been able to prove that none of the preparations which have been recommended and produced in imitation of pollen antitoxin can neutralize the pollen toxin. An antitoxin *cannot* be formed in animals by *feeding* them pollen toxin or pollen. Pollen toxin is a *genuine toxin*, just like diphtheria toxin, and differs from this mainly in that it is thermostabile like snake poison. Pollen antitoxin is a genuine antitoxin just like diphtheria antitoxin.

The *specific* treatment of hay fever is more complicated and more difficult than the treatment of infectious diseases, as, for example, diphtheria. With these diseases the patient is only attacked once by the infective agent, and therefore the treatment has only to combat the result of a single infection; but with hay fever the patient comes in contact with the poison every minute for several weeks at a time. Therefore, the most rational course is to endeavor to obtain an *active immunization* of patients, *i. e.*, to make them immune to the poison. Investigations on animals have shown that this is possible.

The subcutaneous injection of the poison is accompanied by sequences of the most unpleasant sort and is attended with grave dangers, unless done in a most careful manner. But gradual active immunization results through the pollen toxin, while we are producing passive immunization. The cause of this lies in the mode of infection, *i. e.*, that every patient comes into contact with the poison annually for weeks at a time. In the case of diphtheria antitoxin and other specific sera, *passive immunity*

is obtained by subcutaneous injections. It has been shown experimentally that this method is effectual in hay fever. The effect, however, lasts one day at the most. Therefore, it is necessary to inject the antitoxin daily for several weeks of each year. That in itself is not pleasant, and, moreover, it has a specific contra-indication, namely, the occurrence of anaphylaxis. The asserted specific pernicious action of *Pollantin* is connected with this phenomenon. The author sent normal horse serum to those patients who wrote that *Pollantin* irritated them, and without exception he was told that this irritated them just as much as *Pollantin*. This hypersusceptibility was manifested especially in those patients who used the serum in unnecessarily large quantities. These patients can gradually become immunized again to the irritating constituents of horse serum by employing *Pollantin* in a 10 to 20 dilution. The antitoxin is now so strong that traces of serum so diluted are sufficient to protect against an attack of hay fever, provided it is used *strictly* as a *prophylactic*. This is of very special importance but even now comparatively little attention is paid to it.

The pollen antitoxin, *Pollantin*, must be used daily and repeatedly for a long time. In *liquid form* it therefore requires the addition of a disinfectant, but hay-fever patients are very susceptible to all disinfectants. Even the addition of a very small amount of carbolic acid is not well borne. For this reason the attempt was made to prepare a *permanent* preparation by means of *drying*. The sterile antitoxin is dried in a vacuum and ground to the finest powder. In this dust-like form it irritates the mucous membranes of hay-fever patients. This is avoided by the addition of sterile sugar of milk. *Pollantin* is prepared in two forms; namely, as *Pollantinum liqu.*, *i. e.*, sterile antitoxic horse serum with the addition of $\frac{1}{4}$ per cent. of carbolic acid, and as *Pollantinum pulv.*, *i. e.*, dried, sterile, pulverized antitoxic horse serum with the addition of sterile powdered milk-sugar. Both preparations contain only the additions named. Both articles are prepared for spring hay fever and for North American autumnal hay fever, and are only used after the preliminary determination of their antitoxin value, which at present is higher than is necessary for practical purposes.

Individual Predisposition.—Normal persons are absolutely indifferent to the action of pollen toxin. This verifies the correctness of the view that hay fever presupposes an *individual predisposition*. With hay-fever toxin we have for the first time been in a position to conduct experimental investigations on the nature of individual predisposition.

When it was demonstrated that the causative agent of hay fever is a soluble toxin and, therefore, an active physiological-chemical substance, most of the hypotheses which had been advanced as to the factor of hay-fever predisposition fell to the ground. The conception that the symptom-complex was due to influences of a *suggestive* nature was common. Whoever holds this should be convinced by investigations, in which alternately pollen toxin and pure water were used, but in which reaction only appears after the use of the toxin. All explanations to prove predisposition to hay fever a purely *mechanical* affair are made untenable by experiments. One of the most widespread

views is that predisposition to hay fever depends on *local obstruction in the nares or the upper air passages* or on a *local injury to nerves*, as, for example, disease of the trigeminus (ethmoidalis) or of the local sympathetic nerve fibres. All these hypotheses must fail on considering that pollen toxin irritates not only all the mucous membranes of the body, but also the external skin. For a long time it has been believed that the predisposition to hay fever rests on a *gouty diathesis*. This view is not, on the face of it, inconsistent with the pollen theory. Inquiries, however, have shown that gouty persons form only a small proportion of hay-fever patients. Recently, the predisposition has been very generally looked upon as an expression of a *neuropathic disposition*. Hereditary transmission of hay fever is without dispute; nevertheless there seems as much doubt about the neuropathic disposition as of the view of Beard, that hay-fever patients are to be looked upon as *neurasthenic*. *Mental overexertion* is supposed to be of great importance, especially when combined with *responsibility* and *physical overexertion*. In connection with this, it is interesting that the number of men affected is twice as great as the number of women. Hay fever is said to have occurred frequently as an undoubted sequel of infectious diseases like scarlet fever, measles, diphtheria, and after difficult confinements. The relation which exists between *influenza* and predisposition to hay fever commands special interest.

The predisposition to hay fever is to be conceived as an expression of a lesion of the nervous system induced by various causes, and so permanent that spontaneous cures of hay fever are the greatest rarities, and the predisposition is even transmissible. It is remarkable that the predisposition manifests itself by an acquired susceptibility to such a specific substance as the albumin of pollen grains, and further, that hay-fever patients the world over who suffer in spring react to gramineæ toxin, others to the pollen albumin of ragweed and the few other active plants above mentioned, and yet they are totally indifferent to the action of all other plant pollen. The condition seems to be analogous to the *idiosyncrasy* of certain persons to iodoform, shell-fish, etc. The view that normal persons gradually develop immunity to pollen toxin can hardly be considered, for, if this were true, Europeans who go to America in the autumn and are inoculated with the ragweed pollen ought to be susceptible to ragweed, for they practically never come in contact with this pollen in Europe. One might think that pollen toxin, which is not a poison in the usual sense of the word, because it does not act on most persons, only becomes a poison when it enters the body of hay-fever patients. Then the secretions of hay-fever patients would have to contain *activating* substances which are lacking in normal individuals. Investigations on this point have given negative results just as attempts to find an antitoxin against pollen toxin in the secretions and blood serum of normal persons have been negative.

In the writer's opinion, for a time it was regarded as a form of anaphylaxis. This hypersusceptibility might have been caused by the pollen itself; for example, in this manner a patient convalescent from influenza meets with a large amount of pollen which he would normally

have resisted, but which in his weakened condition produces a permanent susceptibility. In the same way the fact that normal persons working with plant pollen suddenly acquire a susceptibility might have been explained. Later experiments have proved that the hyperdisposition cannot be explained on anaphylactic grounds.

Pollen toxin is to be considered a poison which has a specific action on the endings of the nerve fibres of predisposed persons. All studies on the explanation of predisposition to hay fever have to be based on this fact.

Diagnosis.—This rarely offers much difficulty but can be made positively by the ophthalmo-reaction. This consists in the instillation of one drop of a very dilute pollen solution. This seems to differentiate the European from the American form and also to exclude cases of the so-called coryza nervosa. The material is known as *Heufieber diagnosticum* in Germany.

Symptoms.—The annual attacks appear earlier or later according to the condition of vegetation. The illness commences with slight tickling in the canthus of the eye and in the nose, which comes and goes for about a week and at most results in an occasional fit of sneezing. These slight symptoms increase acutely. The conjunctivæ become œdematous. The patient experiences an uncontrollable tendency to rub his eyes, which feel as if grains of sand were in them. The itching is made worse by the rubbing. The eyes begin to lacrimate copiously and photophobia ensues. Sneezing-fits like explosions occur with considerable secretion of mucus, so that several handkerchiefs may be thoroughly drenched inside of a few minutes. The nasal mucous membranes become œdematous; the nasal passages are occluded. Rhinoscopic examination shows intense injection, especially of the small vessels of the turbinate bodies. The original itching gives way to a sensation of piercing burning. As soon as the patient is compelled to breathe through his mouth, the gums and the mucous membranes of the mouth and pharynx begin to itch. An unbearable tickling sensation develops on the soft palate, and later a feeling of rawness, dryness, itching, sticking, and burning appears, which extends from the nose through the posterior nares to the pharynx and Eustachian tubes. Later these symptoms extend to the deeper organs of the throat, and cough with tickling, a scratching feeling of the air passages, hoarseness and a rough voice ensue, until, with a feeling of tension and constriction, shortness of breath begins, which can develop into an asthmatic attack with marked expiratory dyspnoea. Small amounts of tenacious sputum are expectorated, with tormenting straining, and this contains asthma spirals and eosinophile cells. Audible rhonchi soon develop.

The general symptoms may be headache, weakness, exhaustion, depression, ill-humor, languor, tingling in different parts of the body, and an urticarial-like eruption. Digestive troubles also appear in some patients. Some authors claim to have observed albuminuria. If other diseases of the cardiorespiratory system exist at the same time, as tuberculosis or arteriosclerosis, they are made worse during hay-fever time. The plugging of the nose may last for days. As soon as the nose is freed,

the patient begins to sneeze, often as much as a hundred times or more at a stretch. After the patient gets over such attacks he feels so exhausted and depressed that he cannot sit up. He does not sleep for nights in succession because of the tormenting symptoms. A condition of the deepest depression arises, often accompanied by suicidal ideas. The patient feels as if he had fever, but no rise of temperature is demonstrable. The disease occasionally shows sudden remissions; the patient feels perfectly well, only to become severely sick again with great suddenness. The attacks appear to be brought on most suddenly by exposure out of doors, especially in hot, sultry, windy weather. The remissions are produced most rapidly by staying indoors in closed, cool, dark rooms, but also in the open in cool, rainy weather. The suffering usually lasts six weeks. Sometimes, mainly in rainy years, the time may be shorter or it may last eight weeks.

Whoever has once had hay fever experiences an attack every succeeding year; usually the attacks become worse each year until the patient is about sixty, when they begin to abate somewhat. It is rare to find hay fever in children; usually it begins at puberty or later. The Caucasian races, especially the Anglo-Saxons, suffer most, and yet the disease is occasionally seen in the yellow and black races.

Treatment.—The methods of treating hay fever have been greatly influenced by the conceptions predominant at different times. When local changes in the nasal passages were considered to be at the bottom of the predisposition to hay fever, such obstructions were removed by cauterizing, burning, etc. In the bacteria era, antiseptic washes and salves of bichloride, carbolic acid, and boric acid were used. The adherents of the neuropathic and gouty theories directed their measures to such general complaints. After the patient has tried one remedy after another, he usually turns to narcotics, such as chloroform, morphine, and cocaine. Recently adrenalin preparations in combination with cocaine have been much used. In view of the paroxysmal character of hay fever and its natural remissions, it is often difficult to arrive at a definite conclusion as to the value of any treatment. Patients are often delighted that hay-fever attacks disappear after the use of a certain remedy, forgetting that they only began the use of the remedy when the hay-fever season was about to end.

The adherents of the pollen theory advise patients to stay in closed rooms, or to go to regions where there is little vegetation—in the United States, Fire Island, Long Beach, the White Mountains, Green Mountains, the Catskills, and the Adirondacks. Well-to-do patients pass the hay-fever season well at sea. Patients with autumnal catarrh can spend the critical period in Europe without any danger, since ragweed and goldenrod are practically absent.

The introduction of *specific therapy* brought the first change. The specific pollen antitoxin, *Pollantin*, is used in various forms, liquid, powder, or pastilles. The results in several thousand cases show that in about 60 per cent. the treatment was successful, in about 30 per cent. the patient was helped but was not entirely well, and in 10 per cent. there was no benefit.

A thorough test of specific serum therapy in hay fever is very difficult because it takes much larger quantities of antitoxin to combat the fully developed symptoms than would have been required to prevent the onset of the disease. As a rule, only the patient who has full knowledge of the nature of the disease and the mode of transmission of its toxin can be sure of successful results. There are patients who observe no precautions at all, but who, nevertheless, since the use of the serum, have had no attack for several years in succession, and during the last year have done well without its use. These patients must be considered as immunized. This immunization must arise from the protection afforded by the antitoxin against very severe attacks which always leave a much increased susceptibility. If this is successful it arises from the fact that a person comes in contact with the poison every year for weeks at a time and absorbs it gradually to the point of active immunization. But if one is exposed to a severe pollen infection before the immunization has proceeded far enough, recrudescences occur. Intelligent patients who follow this plan with sufficient constancy can expect to build up gradually an active immunity. The different stages in this are plain, for not only do the attacks become fewer and milder, but a diminished susceptibility to the pollen toxin is shown experimentally.

Many patients make the mistake of exposing themselves carelessly to the action of the poison. The aim must be to avoid absolutely severe paroxysms, for only in this way can one hope to attain gradual immunity. It is best to sleep with windows closed, thereby excluding the poison for a considerable time. In the morning one should take the antitoxin before arising, so that it can be absorbed before going out and being exposed to infection. The antitoxin is now of such strength that an amount of the powder about the size of a pinhead, or a drop of the liquid serum, placed in each conjunctival sac and a little more in the nose, is sufficient. The powder is best applied by insufflation. There is a widespread error of using the serum in excessive amounts, thereby mechanically irritating the mucous membranes and increasing the danger of a hypersusceptibility to the serum.

If the serum is conscientiously employed every morning, then it need be used during the day only when signs of irritation appear, and then in small doses. Too frequent doses are not useful. The mistake of omitting the remedy in the morning after a few days' freedom from attacks is just as widespread. Emphasis is laid on the statement that a patient's condition is set back for some time by every attack.

The opinion which has lately been repeatedly published, that Pollantin is of value only in light and moderate cases and not in severe ones is not correct. The worst cases get perfectly well under its use and the patients finally become completely immunized. It is inadmissible to speak of "Pollantin poisoning." Only those patients who are susceptible to normal horse serum are irritated by it. Such persons should use the diluted Pollantin, and only in very small doses. Patients who cannot use Pollantin on account of susceptibility to horse serum can derive considerable benefit from gradually increasing doses of pollen toxin given subcutaneously. An active immunization can thereby be achieved.

CHAPTER XXV

DISEASES OF THE LARYNX

By H. S. BIRKETT, M.D.

THE signs seen in and the symptoms referable to the larynx which come under frequent observation fall naturally into two classes. The first of these embraces signs and symptoms in the larynx which betoken or accompany disease of the body elsewhere, such as the change of the larynx in aneurysm, tabes, syringomyelia, and others which are particularized below. These are frequently of the greatest diagnostic value, and because they are so diverse do not admit of any more complete classification. The second class consists of inflammatory diseases of the larynx and certain manifestations of a neurotic origin.

LARYNGEAL SIGNS AND SYMPTOMS REFERABLE TO OTHER DISEASES

The importance of an examination of the larynx in many diseases cannot be overestimated, for by means of it a diagnosis which otherwise may be obscure is often made clear at once. It happens frequently that there are no subjective symptoms referred to the larynx, but upon examination very definite signs are found. For example, in an obscure case of aortic aneurysm the patient's voice may be absolutely clear, but upon examination a complete paralysis of the left vocal cord is found and the explanation of the absence of any subjective vocal symptoms lies in the fact that the non-paralyzed cord may make such compensatory movement as to definitely approximate the paralyzed cord and bring about the condition essential to clear vocal production. This condition the writer had repeatedly seen when the left vocal cord was paralyzed, due not only to aneurysm, but also to other causes producing pressure upon the recurrent laryngeal nerve, such as an enlargement of the left lobe of the thyroid gland and, rarely, enlargement of the left auricle due to mitral stenosis. Too great stress cannot be laid upon the necessity for careful examination of the larynx in all cases of enlargement of the thyroid gland, especially when operative interference is contemplated, as an absence of such knowledge has led to unfortunate results, namely, damage to the non-affected laryngeal nerve.

Paralysis of the recurrent laryngeal nerve may follow *aneurysm* of the arch of the aorta, or of the right subclavian artery, or may result from enlarged *bronchial lymph glands*; and from the position the nerves occupy in relation to the *œsophagus*, malignant disease of that organ may produce paralysis of the adductors. In enlargement of either of

the lateral lobes of the *thyroid* gland the recurrent nerve may be involved and produce paralysis of both adductors and abductors. The left recurrent laryngeal nerve is more frequently involved than the right.

In aneurysm of the arch of the aorta the evidence of its presence is sometimes indicated by distinct pressure upon and visible pulsation of the wall of the trachea. This pressure is in some cases so great as to produce distinct displacement of the trachea, consequent narrowing of the lumen, and accompanying tracheal stridor.

Chronic inflammation of the *apices* of the lungs, such as tuberculous consolidation and chronic indurative pleurisy, is apt to involve the recurrent laryngeal nerve of either side, but more especially the right one.

In *tubes dorsalis*, the abductors, as proved by Semon, are especially liable to be affected. This abductor paresis is often a very early sign; it is usually bilateral, but may be unilateral. In a patient examined by the writer the only sign was a unilateral (left) abductor paralysis, and in the course of a year he showed definite symptoms of tubes.

In *glosso-labio-laryngeal paralysis* and in *syringomyelia*, abductor paralysis is observed. In *typhoid fever* the vocal paralysis presents no characteristic type, the laryngeal muscles being affected either singly or in groups. The writer has seen the abductors involved in one patient. This is the most common type. "The nature of the paralysis is regarded as a peripheral one, but it is still a matter of dispute whether the muscles, themselves, or the peripheral nerves, suffer a pathological alteration" (Friedrich). In chronic *lead poisoning* either the abductors or adductors may be involved. There is no typical form for the paralysis.

Definite *neuritis* of the laryngeal nerve has followed influenza or exposure to cold winds, resulting in paralysis of any of the group of intrinsic muscles.

INFLAMMATORY DISEASES OF THE LARYNX

Acute Catarrhal Laryngitis.—This may occur as a primary affection or secondarily as an extension of a similar condition of the upper respiratory passages.

Etiology.—The most frequent cause is an undue exposure to cold or a damp atmosphere. Other causes are: Excessive use of or improper method of using the voice; direct injury to the laryngeal structures or indirect injuries by foreign bodies, either within or in the neighborhood of the larynx; inhalation of irritating vapors, to which those whose occupation compels them to inhale dust, such as bakers, stone-cutters, etc., are particularly exposed; sedentary habits; living in badly ventilated rooms; alcoholic excesses; swallowing of corrosive liquids. The gouty diathesis also predisposes to it. It may occur in any of the exanthemata, especially measles and smallpox; it may arise also during an attack of influenza or typhoid fever. Defective nasal respiration acts as a direct exciting cause.

Pathology.—The changes are similar to those of inflammation of mucous membranes elsewhere. The mucous membrane is hyperemic, swollen, and dry looking, especially over those parts where it is loosely

attached, such as the false cords and the interarytenoidean space. This is accompanied by the active production of cell and mucous elements. Sometimes necrosis of the superficial epithelial layer takes place resulting in slight erosion. This is most frequently met with on the edges of the true cords about the middle third, and is occasionally seen on the vocal processes and the interarytenoidean space. Edema may follow.

Symptoms.—In the adult the subjective symptoms are generally very slight. There is a feeling of dryness and irritation of the throat, soon followed by hoarseness, which may increase to complete aphonia. A desire to clear the throat and a dry, tickling cough are present with subsequent expectoration of a small amount of clear mucus, sometimes tinged with blood. Usually there is no febrile disturbance. Objectively, in the very early stage, the true vocal cords lose the normal brightness of their upper surface; later, this condition gives place to the appearance of very fine bloodvessels coursing over the whole length of each vocal cord. In more marked cases this hyperemia becomes uniform, extending frequently into the subglottic region and upward involving the false cords and aryepiglottic folds. At this period of the inflammation the mucous membrane becomes swollen, with the result that the true vocal cords become rounded, especially about the middle third. When the very acute stage has passed the presence of a mucopurulent secretion distributed over the recently inflamed region is to be noted. Upon phonation in the terminal stage of acute laryngitis slight bowing of the vocal cords is seen as the result of a paresis of the internal tensor muscles. In children, owing to the small size of the glottis and the parts about it being less rigid and resistant than in the adult, the disease is apt to produce rather alarming symptoms, such as dyspnoea, which comes on suddenly accompanied sometimes by the pertussis paradoxus. The temperature in children will range from 100° to 102° F., and objectively the whole laryngeal mucous membrane is hyperemic, the bloodvessels on the true cords often being quite distinct. Occasionally, minute hemorrhages are to be seen upon the upper surface of the true vocal cords and in some cases superficial erosions occur on the anterior third of each vocal cord. In children suffering from dyspnoea, who will permit a laryngoscopic examination to be made, the mucous membrane below the glottis is found swollen and bulging toward the middle line. Children who have enlarged tonsils or adenoids, or both, are liable to recurring attacks of acute laryngitis.

Diagnosis.—In the adult the subjective and objective symptoms are quite clear, but it is in children that a diagnosis is not so readily made. The one condition for which it is apt to be mistaken is laryngeal diphtheria. This is generally associated with membrane deposited elsewhere in the upper portion of the respiratory tract, but without the presence of this condition a bacteriological examination of the secretions from the larynx will remove any doubt. The possibility of a foreign body in the larynx being mistaken for acute laryngitis, especially in children, must not be overlooked. The writer saw such a case which had been treated for six weeks for "croup" and upon examination a piece of chicken-bone was seen to be lodged in the subglottic region.

Prognosis.—This is always good in primary cases, but with any of the infectious diseases a more guarded prognosis must be given.

Treatment.—The patient should remain in a room of an even temperature (65°), preferably in bed. Functional rest is most important. Locally, the use of steam inhalations with the compound tincture of benzoin (1 to 10), for five minutes every four hours, is, as a rule, sufficient to relieve most patients. In children the best method of using steam inhalations is by means of a croup kettle. The application of cold to the larynx externally, by means of an ice-bag or ice-coil, is preferred by some. In order to relieve the cough, which often is troublesome, the following will be found beneficial:

R—Menthol	℥j (gm. 4)
Eucalyptol	℥ij (cc. 8)
Ol. menth. pip.	℥iij (cc. 12)

Five drops of this should be placed on a respirator and inhaled for twenty minutes every four hours. If there be any febrile disturbance, small doses of tincture of aconite may be given. It is well in most cases to begin with a saline purgative. In children the symptoms of dyspnoea are sometimes relieved by the use of emetics. The application of heat or cold by means of cloths will sometimes relieve an attack. In severe cases when there are signs of respiratory obstruction, intubation is indicated. Enlarged tonsils and adenoids in children who suffer from recurring attacks of acute laryngitis call for surgical interference.

Chronic Laryngitis.—**Etiology.**—This is usually the result of frequent acute attacks and often of extension of chronic nasal and nasopharyngeal catarrh.

Pathology.—The changes are those of hypertrophy of the mucous membrane, which may be general or local. When affecting the ventricular band, this thickening may be so marked as to hide the true cords; or the changes may be localized to the vocal processes (pachydermia of Virchow), or to the interarytenoidean space. The submucosa is infiltrated with cells and the mucous glands are swollen and distinct.

Symptoms.—Subjectively, the most common symptom is the frequent clearing of the throat in order to remove a huskiness of the voice. In singers the voice loses its timbre and there is a sense of fatigue in the region of the larynx after moderate use. The expectoration is usually tenacious in character, small in amount, and expelled in the form of small pellets of a grayish color.

Objectively, the vocal cords have lost their bright white appearance and vary in color from a pale pink to a bright red and are thickened. This may be limited to the ventricular band, or distinct thickenings may be seen in the interarytenoidean space. Sometimes this hyperplasia of the connective tissue is limited to the subglottic region (chronic subglottic laryngitis). On the surface of the true cords the mucus may be disposed in small pellet-like masses and upon abduction the mucus is drawn into bands stretching across the glottis from one cord to the other. In long-standing cases there is often a paresis of the adductor muscles and an insufficiency of tension. In public speakers, singers, and

teachers, small nodular thickenings, at the junction of the anterior with the middle third of each vocal cord, are occasionally met with.

Diagnosis.—Usually there is not much difficulty in recognition but, as many patients with pulmonary tuberculosis have chronic laryngitis as one of the early symptoms, it is advisable to examine the lungs and sputum of all patients who do not readily improve under local treatment.

Prognosis.—As the tendency of most catarrhal affections of the respiratory tract is to return, one cannot give the same hopeful prognosis as in the acute form. In the case of singers and public speakers one must be very guarded.

Treatment.—As chronic laryngitis is frequently a sequence of chronic catarrhal affections of the nose or nasopharynx, it is of primary importance that unhealthy conditions of these regions receive attention. All forms of obstruction to nasal respiration should have careful attention. Where there is an increase of nasal and pharyngeal secretion, a cleansing solution consisting of bicarbonate and bborate of soda, in the proportion of 5 grains of each to the ounce of warm water, should be used as a spray night and morning. The laryngeal condition should be treated by astringents applied by means of an atomizer. The following are of considerable value: chloride of zinc, 15 grains to the ounce, and argyrol, 40 grains to the ounce. The application should be made once a day. The use of so-called “dry inhalants” is often of benefit, especially in those patients in whom it is difficult to spray the larynx. Any of the following, either singly or in combination, will prove beneficial: eucalyptol, oleum pini sylvestris, and terebene; 5 drops should be placed on a respirator and inhaled for twenty minutes three times a day. When paresis of the intrinsic laryngeal muscles exists, improvement is often followed by the local application of the faradic or galvanic current and the administration of strychnine. Absolute rest of the voice is essential and in many persons a faulty method of voice production will require correction. Attention must be given to the general health; change of climate and occupation assist in the more obstinate cases.

Syphilitic Laryngitis.—This may occur in (a) the acquired, or (b) the congenital form.

(a) **Acquired Syphilis.**—Primary syphilis of the larynx is extremely rare, only two cases having been reported, one by Krishaber in 1877, and the second by Moure in 1890. The lesions are of the secondary and tertiary type, and, concomitantly with these, corresponding cutaneous lesions are frequently found. The period from the primary infection to the development of general infection, as evidenced in the larynx, varies from eight weeks to three months, but the latter may occur as late as twenty or even thirty years after the primary inoculation. The larynx, from its liability to various forms of catarrhal trouble, is especially apt to show lesions of syphilis on account of the lowered resisting power. From the frequency with which men are exposed, through the variety of occupations of life, to catarrhal conditions of the respiratory passages, they are more liable than women to syphilis of the larynx. There is no relation between the character of either the primary or secondary manifestations and the subsequent tertiary symptoms.

Symptoms.—*Objective.*—The most common lesions of the *secondary* stage are: First, erythema; secondly, superficial ulceration; thirdly, a mucous patch; and fourth, condylomata. Upon laryngoscopic examination the mucous membrane will be found either to be uniformly hyperemic, presenting essentially the same appearance as that of an ordinary acute laryngitis; or it may show an irregularity in the distribution of the inflammatory areas, this being due to interposed areas which are non-vascular, and the whole picture presenting a so-called “mottled” appearance, which, as some authors maintain, is definitely characteristic of secondary syphilis. The areas involved are generally the epiglottis and the false and true cords. This inflammatory process may lead to a destruction of the superficial layer of the mucous membrane, in which case there will be seen a small shallow and irregularly shaped ulcer whose surface is covered with a yellowish colored secretion. The superficial ulcers may extend and unite with others and when healed leave a very thin, stellate-looking cicatrix. The occurrence of the mucous patch within the larynx is comparatively rare. The laryngeal patch is rounded, oval, or oblong in outline, of a whitish-gray or yellowish color, and surrounded by an area which is very hyperemic. The localities in which such a patch may be seen are the laryngeal surface of the epiglottis and its edges, the arytenoepiglottidean fold, the false and true cords. Condylomata in the larynx appear as rounded or oval elevations with a yellowish-colored surface.

Tertiary syphilis manifests itself in three forms: gumma, ulceration, and cicatricial tissue. These conditions exhibit themselves within a period varying from three to twenty or more years after primary infection. The gumma presents itself as an infiltration varying in size from that of a very small pea to a size sufficient to produce obstructive symptoms. In appearance the mucous membrane covering it may be of a normal or darker hue, elevated above the surrounding mucous membrane, and its base presenting an area of inflammation of a deep rose color. It may be found on the laryngeal surface and edges of the epiglottis, the arytenoepiglottidean folds, the interarytenoidean space, the false cords, and the subglottic region. The lesion is usually single but may be multiple. With the progress of time the gumma undergoes a retrograde metamorphosis, as a result of which it becomes yellowish in color, and at last, breaking down, presents the stage of ulceration.

The ulcer has generally a circular outline, the edges of which are ragged and thickened, a surface excavated and covered with a dirty yellowish-colored secretion, and a base displaying a zone of hyperemia. If neglected, the inflammatory process may extend to the deeper-lying structures, and a perichondritis, with subsequent abscess formation, necrosis of the cartilage and its exfoliation, may ensue. Perichondritis may, however, occur without ulceration. It is in this stage of ulceration that dangerous symptoms are apt to supervene. Oedema, either acute or chronic, may arise and produce symptoms of marked dyspnoea, or the exfoliated cartilage may obstruct the respiratory tract; or the loss of the cartilage, especially if it be a portion of the thyroid, cricoid, or arytenoid, may lead to such collapse of the larynx proper as to interfere

very materially with respiration. The epiglottis may be involved to such an extent as to interfere with the process of deglutition and allow portions of food to enter the larynx. Fixation of one or both cords, as a result of perichondritis or chondritis, may lead in some cases to a narrowing of the rima glottidis and consequent dyspnoea. Myopathic paralysis of the abductors is not of uncommon occurrence but of very serious moment when present. Finally, hemorrhage may occur and even result fatally, but, fortunately, this happens rarely. A condition described by Fournier as parasymphilitic laryngitis is not uncommon and is characterized by a general fibroid hypertrophy of the mucous membrane of the larynx. It may also be localized to such areas as the false or true cords, or the interarytenoidean space. The chief feature of this pathological condition is its obstinacy to treatment.

The final step is cicatrization. The less extensive cicatrization is evidenced by a white stellate scar of varying extent. The results of ulceration and cicatrization of adjacent structures often lead to the epiglottis being bound down to the base of the tongue or to the posterior or the lateral walls of the pharynx. Bands may be stretched across the lumen of the pharynx and by their contraction lead to great distortion of the structures. Adhesions between the vocal cords may result in web-like bands, which may involve the glottis to a greater or less degree. The cicatricial process may be so severe as to convert the larynx into a mass of cicatricial tissue with a small perforation in the centre acting as the glottis.

Subjective.—In the *secondary* stage they are usually those of a severe, acute laryngitis. The voice is husky or may be aphonic, there is a moderate cough and expectoration of a small amount of tenacious secretion; and, if the epiglottis be involved, deglutition may be painful. In the *tertiary* stage the symptoms are more pronounced; the voice varies from slight huskiness to complete aphonia. Dysphagia is more frequent owing to the involvement of the epiglottis in the inflammatory and destructive processes. Occasionally food finds its way into the larynx when the epiglottis has been considerably destroyed.

It is in the tertiary stage that sudden oedema is apt to supervene, and it may produce such grave symptoms of stenosis as to necessitate immediate tracheotomy. When a suppurative process is going on in the larynx there is marked general disturbance, the temperature rising from 101° to 103° F. Externally, the perichondritis or suppurative process may be marked by swelling and tenderness over the affected part; with destruction of the cartilage and its exfoliation there is always danger of the exfoliated portion obstructing respiration. The breath, when the disease has reached such a stage, is usually very offensive. The expectoration is mucopurulent in character, sometimes tinged with blood, and it may contain fragments of necrotic tissue.

Diagnosis.—The Wassermann reaction is of great value. It is the diffuse laryngitis of the secondary stage that alone requires differentiation from the non-specific acute catarrhal laryngitis. Objectively, there may be at times, and especially when the inflammation is uniformly disposed, considerable difficulty in deciding which of the two conditions is present.

The non-specific form of laryngitis yields to the usual methods of treatment, while one should be suspicious of a laryngitis which resists such treatment. A laryngitis in a tuberculous subject may also resist local treatment, but an examination of the general condition and the sputum will materially aid. It is, however, rather in the ulcerative form that difficulties present themselves. The diseases from which syphilis of the larynx requires to be differentiated are tuberculosis and carcinoma. In *tuberculosis* the ulcers are apt to be numerous, the outline not so sharp or distinct, the edges less indurated, the surface not so deeply excavated, and the granulations pale and indolent-looking. The mucous membrane of the soft palate, pharynx, and larynx is pale; there is some febrile disturbance, with increased rate of pulse, and the general appearance of the patient is that of anemia. Smears from the ulcerated areas will often show tubercle bacilli, and an examination of the expectoration will generally give a like result. The two diseases may coexist and an ulceration originally syphilitic may become tuberculous.

In *carcinoma* the difficulty is greater; here a new growth precedes the stage of ulceration and it is in this latter condition that the difficulty so often arises. In carcinoma the disease presents itself as an ulcerating outgrowth more frequently than as a true, deep, excavating ulcer as in syphilis. The ulcerating outgrowth is more vascular and the surrounding inflammatory area of a deeper color than in syphilis. The progress of a carcinomatous ulcer is much slower than that of a syphilitic one. Other subsidiary points which are frequently considered are: the age, the presence or absence of enlarged glands, and the existence of pain; but these afford very little support to either view.

Microscopic examination of a removed portion is often doubtful in its results, but should be done. In doubtful cases recourse to anti-syphilitic remedies may clear up the difficulty, and yet one must not be too sanguine as to the ultimate results, for iodide of potassium has often the effect of producing absorption of the inflammatory products in cases of carcinoma and thus materially altering the picture. One is sometimes confronted with the further difficulty of finding syphilis and carcinoma coexisting.

Prognosis.—This, in any given case of syphilis of the larynx, depends upon, first, the absence of any other coexisting disease (tuberculosis and carcinoma); second, the extent of the existing lesions, and third, the faithfulness with which the patient will follow treatment. In the secondary lesions, recovery usually takes place without any noticeable changes; in the tertiary stage, when ulceration is present, the progress is usually readily arrested and the function of the larynx interfered with only so far as the destructive process has extended. When cicatrization has occurred, very little improvement is to be expected.

Treatment.—This, by salvarsan or neosalvarsan, is beyond the stage of experimentation. Its effects upon all stages of the disease, except cicatrization, are so rapid and so marked that its use is indicated as a preliminary method of treatment to be followed later on by mercury and iodide of potassium.

Locally, alkaline sprays, such as Dobell's and Seiler's, and sedative

inhalations (compound tincture of benzoin), are indicated, and, after the subsidence of the acute stage, applications of weak solutions (1 to 20) of nitrate of silver. When gummata or ulcerations are present, iodide of potassium in increasing doses is indicated. Cleansing the ulcerated area with alkaline and antiseptic sprays and the subsequent application of a solution of nitrate of silver, or the insufflation of iodoform will assist. Vegetations may require the use of the curette, forceps, galvanocautery, or chromic acid, to hasten their disappearance. Neither general nor local treatment avails when fibroid changes with extensive hypertrophy have taken place. Adhesions, fibrous bands or membranes, and stenosis of the larynx, require surgical interference.

When syphilis and tuberculosis coexist it is generally agreed that the syphilitic element should first receive treatment. In all forms of syphilis of the larynx smoking and the use of alcohol in any form should be prohibited.

(b) **Congenital Syphilis.**—The larynx may be involved at any age, but the disease more commonly shows itself within the first six months after birth. As to sex it is more frequently met with in the female—in the proportion of three to one (Mackenzie). Three distinct forms are to be met with: In the first, the lesions involve the mucous membrane and the submucosa; in the second, the lesions involve the deeper structures and are characterized by extensive ulceration rapidly involving the cartilaginous frame-work of the larynx; in the third form, there is a deposit of dense fibrous tissue leading to contraction and stenosis.

Symptoms.—In the early stages the symptoms are those of an intense laryngitis, the voice being quite hoarse; nothing more than a very marked hyperemia of all the laryngeal structures is observed. The coexistence of cutaneous syphilis is frequent. In the second form, the ulceration involving the epiglottis and laryngeal structures is increased and the cry of the child is extremely hoarse and more deeply pitched than in the early stage. The cough is harsh and paroxysmal, leading frequently to an attack of vomiting; deglutition is often difficult. In the third variety the voice is almost aphonic and, in consequence of the lumen of larynx and trachea being considerably reduced, there is marked respiratory difficulty which may be accompanied by cyanosis and convulsions.

Diagnosis.—Early forms of the disease may be mistaken for simple laryngitis, but often there are other symptoms of the inherited form to be seen in the skin and mucous membrane of the mouth and throat. In the more advanced form, the evidence of the disease may be found in the state of the teeth, the condition of the eyes, and cicatrices about the angles of the mouth. The Wassermann test is of great aid.

Prognosis.—This is always grave, but less so in the early stages when, if the affection be recognized and treated, favorable results may be looked for. In the later forms, even when its true nature is recognized, treatment seems to produce less effect than in the acquired form.

Treatment.—Salvarsan has proved of great benefit, particularly in the ulcerated forms. It is not to be used exclusively but should be followed by a course of mercurial inunctions. Pulv. hydrargyri cum

creta, gr. $\frac{1}{4}$ or $\frac{1}{2}$ (gm. 0.016 to 0.03), may be given three times a day for several weeks. General tonic treatment should follow.

Tuberculous Laryngitis.—**Etiology.**—The primary cause is the entrance of the tubercle bacillus into the tissues of the larynx. Tuberculous laryngitis may be either *primary* or *secondary*. Primary tuberculous laryngitis is very rare. Secondary tuberculous laryngitis occurs in about 10 per cent. of the cases of pulmonary tuberculosis.

Pathology.—Three stages usually can be recognized: First, hyperemia or anemia of laryngeal structures, associated with an exudate of mucus, pus cells, and desquamated epithelium. Second, a state of infiltration, in which a deposit of minute nodules of diseased tissue, tubercles, takes place, most frequently in the aryteno-epiglottidean folds, interarytenoid-eaen space, vocal cords, the ventricular bands, and the epiglottis. The third stage is that of ulceration. The tubercles break down; the ulcerations are at first superficial, but through infection with pyogenic cocci become deeper and more extensive and probably play an important rôle in the production of perichondritis.

Symptoms.—*Subjective.*—These depend upon the seat and extent of the invasion. If the intralaryngeal structures are involved, the only symptom may be alteration of the voice ranging from slight huskiness to aphonia. If the epiglottis or aryteno-epiglottidean folds are involved the chief symptom is dysphagia. Cough may or may not be paroxysmal, and is often preceded by a tickling sensation; there is expectoration of a clear or yellowish-colored mucus—as the laryngeal condition is nearly always associated with pulmonary involvement; shortness of breath is not uncommon; a varying degree of fever (99° to 103° to 104° F.) and a rapid pulse are often present. Functional aphonia (paresis of the adductors or the internal tensors of the cord) associated with general debility, is occasionally met with in early cases of pulmonary tuberculosis.

Objective.—These depend upon the stage in which the patient is suffering. In the early or catarrhal stage the mucous membrane of the larynx may be frequently hyperemic or anemic. If hyperemic there is frequently with it a marked anemia of the soft palate and pharynx and, what is almost peculiar, an extremely irritable state of the throat on laryngoscopic examination. In the stage of infiltration the areas most frequently involved are the aryteno-epiglottidean folds. They are swollen, pyriform in shape, a pale pink or red in color, and the swelling often is so great that they are in contact with the posterior and lateral walls of the pharynx. The interarytenoid-eaen space, when involved, shows distinct thickening of the mucous membrane, which upon phonation is thrown up into papilli-form projections and if the infiltration be sufficiently large it may prevent the approximation of the vocal cords. The surface of the infiltration is often occupied by an ulceration; springing from its base small granulomata may be seen.

Next in frequency of involvement is the epiglottis, which when uniformly infiltrated assumes a turban shape, and often is sufficiently swollen to prevent a view of the interior of the larynx. It is usually of a red color; the ulcers, which are generally situated on the edge and laryngeal surface of the epiglottis, are deep, and the surface covered with a slough.

The ventricular bands may be invaded and swollen; this generally breaks down and leaves a deep ulceration. The vocal cords may present, in addition to an ordinary acute catarrhal state, an infiltration or ulceration. When infiltrated they are swollen, uneven, and hyperemic. If this be confined to one cord it is strongly suggestive of tuberculosis. Ulceration, when present, occurs most frequently on the edges and over the vocal processes. It may be so extensive as to destroy the vocal cords. The mobility of the vocal cords may be impaired, either from extension of the disease into the crico-arytenoid joint or from involvement of the recurrent laryngeal nerve, or some of its branches, by pressure or neuritis.

Diagnosis.—Laryngeal tuberculosis is generally associated with advanced pulmonary disease, and when such is the case there is usually no difficulty in recognizing the laryngeal lesion. In a small number the pulmonary disease is not easily detected and diagnosis is more difficult. There are some patients who have a slightly irritating cough without expectoration, catarrhal laryngitis, which has resisted all treatment, anemia of the soft palate and larynx, a slight elevation of evening temperature, but no physical signs of tuberculosis. Such patients should be tested with tuberculin. The two diseases which may resemble laryngeal tuberculosis are syphilis and carcinoma. The differential diagnosis is discussed under Syphilitic Laryngitis.

Prognosis.—This must be guarded, as the laryngeal lesion is only a local expression of pulmonary involvement and the improvement of local conditions depends very greatly upon that in the lungs.

Treatment.—Too great stress must not be laid upon the effect of local treatment in laryngeal tuberculosis. It is undoubtedly influenced by any improvement made in the pulmonary condition.

All tuberculous conditions of the larynx should receive a preliminary cleansing by means of an antiseptic and alkaline lotion, before carrying out any direct local treatment. In the acute catarrhal stage the use of inhalations (compound tincture of benzoin, eucalyptol, terebene, 1 to 150), or a spray containing menthol or chloretone (1 to 25), is beneficial in relieving the cough and moderating the expectoration.

When ulceration is present, the application once a day of menthol in olive oil (10 to 20 per cent.) is of considerable benefit. Lactic acid in glycerin (50 per cent.) is useful in cases where there is a sloughing surface. Either of these applications should be made by means of a cotton-wool swab, rolled upon a suitably curved applicator and guided to affected parts by means of the laryngeal mirror. Care must be taken that the cotton-wool is not charged with more of the application than it can hold, otherwise the superfluous amount will find its way into the trachea and produce an attack of violent coughing or even spasm of the glottis. These applications are more readily made in irritable throats after a preliminary spraying with a 5 per cent. solution of cocaine.

The occasional use (once a week) of puncture of infiltrated or ulcerated areas by means of the galvanocautery, has proved to be useful. When the epiglottis and aryepiglottidean folds are infiltrated or ulcerated and dysphagia is marked, this may be relieved by insufflations of small quantities (5 grains) of orthoform. To obtain relief to the dysphagia by

means of a spray of cocaine is not advisable because of the limited time of local anesthesia produced and also from the disastrous effects resulting from its absorption.

When there is œdema of either the epiglottis or aryepiglottidean folds, relief is often obtained by puncturing the swollen tissues with a guarded laryngeal knife under the guidance of the laryngeal mirror. Dysphagia due to such conditions is often relieved by injecting 1 cc. of 90 per cent. alcohol into the superior laryngeal nerve at a point where it pierces the thyrohyoidean membrane. More recently Cholier and Bonnet¹ have resected the superior laryngeal nerve for the relief of the dysphagia with very good results.

The question of climate in laryngeal tuberculosis is one upon which authorities differ very much. In England it is the opinion that patients with tuberculosis do not do well in high altitudes, while in Canada and the United States the opposite view is held. In selecting a climate for such patients the absence from irritating dust is of more importance than altitude. It is advisable that the patient be kept under direct laryngeal treatment. Vocal rest is a very necessary adjunct.

Œdematous Laryngitis.—(Edematous infiltration of the larynx may occur in two forms: (1) *Primary*, which may be subdivided into (a) the non-infectious form—a variety is described by Strübing as an angioneurotic œdema—and (b) the infectious form. (2) *Secondary*.

Etiology.—The non-infectious form is caused by local injuries, the action of corrosive liquids, inhalation of steam, and the internal administration of iodide of potassium, even in small doses. In the angioneurotic form no cause has been found. It occurs in persons of a neurotic temperament and certainly is hereditary, as shown in the remarkable series of cases reported by Osler in 1888. Worry, mental excitement, anxiety, and fright are doubtless causes. The writer has seen œdema of the uvula and soft palate follow the administration of an immunizing dose of antitoxin. It is generally associated with œdema of the skin. In the infectious form it is due to the action of pathogenic bacteria.

In the secondary form the causes are those diseases which frequently produce a perichondritis: tuberculosis, syphilis, and carcinoma, typhoid fever, scarlet fever, measles, smallpox, and gonorrhœa (rare). It may also occur in the course of a peritonsillar abscess or an inflammation at the base of the tongue. It may also arise from chronic valvular disease, chronic nephritis, and as a passive congestion from pressure on the veins of the neck.

Pathology.—(Edema of the larynx is characterized by a serous infiltration of the submucous cellular tissue. In the traumatic cases it is usually unilateral, involving the epiglottis and aryteno-epiglottidean folds. In its disposition it differs from the secondary form, which is always bilateral or symmetrical. In the infectious form the infiltration is either seropurulent or purulent. Angioneurotic œdema depends upon an increased irritability of the vasodilator nerves, due either to direct or reflex, central or peripheral disturbance. A spasmodic contraction of the vessels

¹ *La Presse Médicale*, Lyons, November 9, 1912, 92.

is followed by a paralytic dilatation and stasis or retardation of the circulation; serous exudation ensues, producing acute œdema (Kocher).

Symptoms.—*Subjective.*—The patient usually complains of slight difficulty in swallowing and a feeling of fulness in the throat. The voice becomes husky and, as the œdema increases, it becomes more deeply pitched and inspiration and expiration more difficult and stridulous in character. A distressing and irritating cough is often present. The pain accompanying deglutition often shoots up toward the ears. The swelling of the epiglottis and of the aryteno-epiglottidean folds is often so great that these structures lie in contact with the posterior and lateral walls of the pharynx, and liquids may find their way into the larynx. In the infectious form the local condition is generally preceded by a chill or rigor and followed by a rise in temperature (101° to 104° F.). In this form the sequence of events is rapid and prostration most marked. In angioneurotic œdema of the larynx the symptoms appear suddenly, coming on sometimes during sleep, and may be so severe as to end fatally.

Objective.—Upon examination with the laryngoscope, the epiglottis is swollen and turban-shaped, often so much so as to obstruct the view of the larynx; the aryteno-epiglottidean folds fill up the pyriform sinuses and the mucous membrane is tense and glistening. The false cords, when involved, are swollen and the color of the mucous membrane of a deeper rose color than that covering the aryteno-epiglottidean folds and epiglottis. Owing to the mucous membrane of the true cords being intimately attached to the cords, there is little swelling; but just below the cords (*i. e.*, infraglottic), where the mucous membrane is loosely attached, the œdema shows itself by distinct swellings.

Prognosis.—This depends upon the cause and extent of the œdema. In the non-infectious cases it is favorable, but in the infectious forms it is most grave. In the secondary form it depends upon the gravity of the primary lesion.

Treatment.—Absolute rest in bed is imperative. The room should be warm and the atmosphere moistened with a steam spray, vaporizing the compound tincture of benzoin (1 to 20). No use of the voice should be allowed. Locally, cold, by means of a coil or ice-bag, should be applied to the neck. The use of small pieces of ice dissolved in the mouth is not advised, as by the time it reaches the involved parts the ice has become nothing more than warm water. A spray of adrenalin chloride (1 to 5000) will often lessen the œdema. Should the obstructive symptoms not abate, the swellings should be punctured by means of a guarded laryngeal knife, guided by the laryngoscope. The throat should be rendered anesthetic by a 10 per cent. solution of cocaine. Pilocarpine, given hypodermically (gr. $\frac{1}{10}$ to $\frac{1}{4}$, gm. 0.006 to 0.016) has occasionally proved beneficial.

When the symptoms are not relieved by the foregoing treatment, tracheotomy should be performed without any further delay. Intubation is not to be recommended, as the swelling is apt to be so marked as to envelop the opening of the tube when in position.

In angioneurotic œdema, the patients, being highly neurotic, require assurance, and all sources of anxiety and worry should be removed.

Laryngismus Stridulus.—This is a spasmodic contraction of the intrinsic muscles of the larynx leading to closure of the glottis.

Etiology.—*In children* it occurs most frequently between the ages of six months and a year, seldom after seven years of age; it is more common in males than females. These children are usually ill-nourished, badly developed, and often rachitic. Faulty digestion, intestinal parasites, delayed dentition and certain conditions of the pharynx and nasopharynx, such as enlarged tonsils and adenoids, act as causes. In excitable children it may be brought on by violent crying. It is sometimes hereditary.

In adults it may occur as the result of irritation of the trunk of the pneumogastric nerve or its branches, from enlarged bronchial glands, mediastinal growths or aortic aneurysm; elongated uvula or enlargement of the lingual tonsil. In locomotor ataxia it may occur, constituting the so-called laryngeal crisis. It may also occur as an hysterical phenomenon.

Symptoms.—In the child the onset is sudden, coming on during sleep, while the child is playing or during crying. The inspirations are short, frequent, and gradually the stridulous character becomes more marked. In a few seconds the short, stridulous breathing gives way to a whistling inspiration and the attack ceases. The child's face becomes livid, the back and neck are arched, the thumbs flexed upon the palms, the hands on the wrists and the feet flexed and turned inward; consciousness ceases. The spasm may be so severe that the glottis is closed and respiration stops. The face now becomes of an ashy hue and perspiration breaks out on the forehead. The spasm may last from a few seconds to a minute and, when too prolonged, death ensues. The younger the child the more severe is the attack and the more likely to prove fatal. In the adult the attack is similar although much less severe.

Prognosis.—Usually this is good except when the attacks are severe, frequent, or occurring in a very young infant. A rachitic constitution makes the prognosis less favorable.

Treatment.—The condition should be regarded as a local manifestation dependent upon some local or constitutional cause. *During the attack*, the child should be immersed in a hot bath up to its chin; a small quantity of mustard in the bath will act as a diffusible stimulant. Should the spasm be a severe one, a few whiffs of chloroform will often give relief. If the attack be attended with symptoms of impending death from suffocation, intubation or tracheotomy, preferably the former, should be performed. *In the interval*, attention should be given to correcting any existing general dyscrasia, especially rickets. Any gastric or intestinal disorder should be rectified and the child placed in good hygienic surroundings. The administration of general tonics is desirable, especially cod-liver oil; the syrup of the iodide of iron in the strumous subject, and in the rickety child small doses of phosphorus are of great value. In the adult careful examination should be instituted to ascertain the cause and, if possible, rectify it.

CHAPTER XXVI

DISEASES OF THE BRONCHI

By ALEXANDER MCPHEDRAN, M.D.

BRONCHITIS

Definition.—Bronchitis is usually defined as a catarrhal inflammation of the bronchial tubes, but the term is equally applicable to any other form of inflammation. All the layers of the bronchial wall are frequently involved in the inflammatory process.

Etiology.—Bronchitis occupies but little space in medical literature or in the text-books, and in the clinic usually has little consideration. Patients themselves think it of little importance, and usually only seek advice for cough. Yet it is not only one of the most common, but also one of the most important and interesting of diseases.

The usual division into *acute* and *chronic* is useful, and, in general, correct, although there is no definite line of demarcation, the one gradually merging into the other; yet the distinction between the two is well marked. In *chronic bronchitis* there are definite connective-tissue changes in the bronchi, or a constitutional state lowering vitality and rendering such changes liable to occur, so that infection, although important, plays only a secondary part in its causation; while in *acute bronchitis*, on the other hand, *infection* plays the chief rôle.

Coryza and cough, which so often are the harbingers of acute bronchitis, are known as a "*cold*," and are popularly attributed to chilling, as is also acute catarrh of all parts of the respiratory passage. This view is no better grounded in the case of these diseases than it was a few decades ago in general medical teaching as the cause of pneumonia and rheumatic fever. In all these diseases, in acute catarrhs especially, chills in many cases play an important, although only a contributing, part; but in the majority of cases there has been no chill or exposure to cold. All catarrhs are caused by infection and spread by contagion, as shown so frequently by their infecting whole households. The infectious nature of catarrhal diseases of the respiratory passages is also shown in some epidemics of coryza and bronchitis by the occurrence in some members of the family at the same time of acute tonsillitis, in others of intestinal catarrh, especially among the children. In crowded and unsanitary conditions epidemics occur in which colitis is met with at the same time as catarrh of the respiratory passages, and even bronchopneumonia; both affections may occur in the same child.

Epidemics of coryza and cough occur, as also do other infectious epidemic diseases, especially in spring and autumn, the time of cold, damp

weather, and seldom during the clear, frosty winter. Epidemics of catarrhal fever, with general aching pains and disturbances, are spoken of as "grippe." This term is often used synonymously with "influenza." As the latter is due to a specific infection, the influenza bacillus of Pfeiffer, it should not be confused with catarrhal fevers of other kinds, as it is a specific disease, and often attended with very serious results, as cardiac weakness, prolonged prostration, bronchiectasis, etc.

The ordinary catarrhs of the respiratory tract above the larynx are usually the result of a variety of infectious organisms; below that it is more frequently a single organism which is the chief exciting cause of the catarrh, although two or more are not rarely associated. It is probable that any of the pathogenic microorganisms capable of causing inflammation may, under favorable conditions, cause bronchitis. In a case at present under observation, the patient has had two attacks of bronchitis with a short interval between them. In the first, the *micrococcus catarrhalis* was the chief infectious agent, a few cocci and bacilli of indefinite character also being present; in the second attack, *pneumococci* and *streptococci* occurred in large numbers, and a few micrococci catarrhalis and staphylococci. This patient has been subject to similar attacks, and in the preceding one, two years before, micrococcus catarrhalis was the chief organism.

The *micrococcus catarrhalis* is a large organism occurring as a saprophyte in the mucous membrane of the air passages. It often becomes pathogenic in man, and may cause influenza-like attacks, as it did in the case cited above. It is usually present in the sputum of both acute and subacute bronchitis, and in bronchopneumonia usually in association with pneumococci, streptococci, staphylococci, and also the influenza bacillus.

Of the pathogenic organisms causing acute bronchitis, those most frequently found are pneumococci and streptococci, the former occurring probably oftener than the latter, in both mild and severe cases. The influenza bacillus is one of the most important causes of bronchitis and bronchopneumonia. However, like the diphtheria bacillus, it is often differentiated with difficulty from similar bacilli found in various diseases of the bronchi and lungs, other than those due to influenza. Wassermann¹ has pointed out that failure to find the influenza bacillus does not exclude the possibility of the disease being influenza, as it may be present early in the disease and disappear within a few days. Many other bacteria have been found in bronchitis, such as the staphylococcus, Friedlander's bacillus, diphtheria bacillus, bacillus pyocyaneus, micrococcus tetragenous, bacillus coli communis, and a variety of other undetermined cocci and bacilli. Of course, it is doubtful how far all of these are the causes of bronchitis and not avirulent bacteria present in the secretion. In view of these facts, it seems evident that in acute bronchitis the extent and severity of the disease, and especially the peculiarities of its course, are due chiefly to the nature and virulence of the infection. In addition to these known causes there are other various infectious

¹ *Deutsche med. Wochenschr.*, 1900, No. 28, 445.

agents which are as yet not determined; among these are especially the infectious agents causing measles and whooping cough.

The Bacteria of the Normal Air Passages.—The question naturally arises whether the normal air passages are sterile or the habitat of bacteria, as are the mouth and large bowel. Great masses of bacteria are found in the healthy nasal cavities; they may be pathogenic. In the anterior nares, the vibrissæ, and the lower parts of the mucous membrane are rich in bacterial flora, which have been abstracted from the inspired air; in the upper and back parts, the organisms rapidly diminish in healthy conditions. The mouth and throat contain many organisms of various kinds; the larynx lodges few. In the trachea the number quickly lessens. Most of the small bronchi in animals, and doubtless also in man, are probably free of bacteria, although a few non-virulent ones may occur in parts here and there. After tracheotomy in animals bacteria early enter the trachea and bronchi, and lead to inflammation of the mucous membrane, and often later of the lungs; this must be quite as true also of man.

That in inhalation, especially forced, dust rich in bacteria reaches the finer bronchi and even the alveoli is certain, but in the sound lung the inhaled microorganisms are usually soon removed from the tissue, made harmless, and die; while the coal and other dust particles remain in the lung tissue, as well as in the lymph vessels and glands. That these sparse, scattered, and weakened germs which are found here and there in the sound lung and bronchi may, under certain conditions, such as chilling, become pathogenic and virulent as in pneumonia, is indeed possible, but probably not of frequent occurrence. Irritant gases inhaled for a short time by animals produce congestion of the bronchi, with free exudate, but the secretion being sterile is soon absorbed and the mucous membrane restored to normal. If the inhalation is long continued, organisms from the nose and throat, as well as those from without the body, gain entrance to the bronchi and even the lungs, and an inflammation may result.

It is an error to assume that the organisms normally in the nasal cavities are usually the infectious agents in the bronchi and lungs; much oftener the infections are exogenous, the endogenous ones usually lacking virulence. The same is true of puerperal conditions, in which there is much more danger from contact infection from without, than from organisms normally existing in the vaginal tract. In healthy individuals certain aids to the virulence of most germs are necessary to enable them to excite inflammation in the respiratory tract. Many organisms, especially in the nose, or even in the lungs, die early or become avirulent; others become infective only after their virulence has been increased, or they are aided by favorable conditions.

Though infection plays the important rôle in diseases of the respiratory passages, yet other factors which aid in the production of the disease should not be overlooked. Wetting and chilling, formerly regarded as efficient causes of bronchitis, pneumonia, etc., have been proved by investigation to be not more than of secondary importance in the production of these diseases. In many cases they play a necessary part, in

that they create a condition without which the infecting organisms would be powerless to excite the disease. Bacteria, however, in most instances cause bronchitis without the aid of chill, while chill never causes bronchitis in the absence of infecting organisms.

Many years ago Brunton pointed out that the application of ice to the chest and abdomen of a rabbit caused blanching of the bronchial mucous membrane owing to stimulation of vessel walls. In a short time the contraction of the vessels gave way and dilatation followed, with increased secretion of mucus. F. Müller¹ found that if a rabbit is wet with cold water and then exposed to a strong cold draught in a partially opened window, the body temperature is lowered and the animal becomes ill, but recovers in a few hours, if the observation has been properly carried out. If the animal is killed soon after the cooling, in the bronchi a great increase of secretion will be found obstructing the small tubes, and their alveolar areas either collapsed or filled with œdematous exudate. There was no leukocyte infiltration, proving that the exudate was not inflammatory. No bacteria, or at least very few, were to be found in the affected lung or bronchi. In a few cases after the chilling a severe illness resulted, and in the lungs were found peribronchial inflammation, or even pneumonia, with marked leukocyte infiltration and many bacteria. In these animals no doubt virulent bacteria were already in the lungs before the animals were exposed to chilling.

In man, *chilling* may cause a similar series of consequences. On account of the clothing and the greater size of the body, such marked chilling in man rarely occurs, and, therefore, marked secretion from the bronchi without inflammation is not often met with. Yet in people with irritable respiratory tracts, cough with slight expectoration and without illness, not infrequently occurs after chilling. This is especially true of the nose, throat, and larynx, which are usually not quite normal. However, that in healthy persons even marked chilling in absence of infection causes no injurious results is shown by the experience of explorers in Arctic regions. Nansen and his associates did not suffer from any of the diseases ordinarily attributed to cold, although the exposure was often extreme. It was only after their return to a temperate, and therefore a germ-laden atmosphere, that coryza, bronchitis, and pneumonia affected them without any chilling, and, their immunity having been diminished by their long absence, they became very susceptible to these and other infective diseases, and many of them suffered very severely.

The experiences of the members of the Shackleton expedition to the South Sea are even more instructive. Although much exposed to extreme cold and privations they had no catarrhal affections until a bale of clothing was opened for distribution. Almost immediately there was an outbreak of catarrhal inflammation of the respiratory passages from which none of the members of the company escaped. The infective micro-organisms had evidently lain dormant in the bale and were set free when the clothing was shaken out. A similar outbreak occurred later when the ship's carpets were taken up and shaken.

¹ *Deutsch. Klinik.*, 1904, p. 233.

Bronchitis is a common complication of *typhoid fever*. The adynamia of this and other diseases of marked prostration favors the occurrence of bronchial infection. But in the early stage of typhoid fever, before adynamia occurs, bronchitis is a frequent symptom, of which the bacillus of Eberth is the possible cause.

Bronchitis is also of common occurrence in various other adynamic and *cachectic states*, as infective endocarditis, cholera, scurvy, diabetes, chronic nephritis, chronic alcoholism, carcinoma, etc. It is very frequent in the cachexias of the infant, whether of gastro-intestinal, tuberculous, or syphilitic origin.

Pathology.—Simple uncomplicated bronchitis is so rarely fatal that the opportunity of examining the pathological changes in bronchial mucous membranes occurs very seldom. Of the various layers which compose the walls of the trachea and bronchi, the mucous membrane alone is usually the seat of morbid changes. On postmortem inspection there is often singularly little to be seen in acute bronchitis. There may be more or less congestion of the lungs, and patches of collapsed lobules surrounded by areas of emphysema scattered here and there.

At the outset the superficial epithelium is largely converted into muciparous cells. For this reason the expectoration at first consists of glairy, transparent mucus, which may be scanty (dry catarrh), or abundant and more liquid (serous catarrh). The muciparous cells are not only greatly increased in the large bronchi but also in the medium and fine bronchi (Müller). The mucous glands which exist only in the large bronchi are also affected, so that the mucous secretion of the larger tubes greatly exceeds that of the small ones in which there are no glands.

Microscopically, sections through an affected bronchus show œdema, congestion, and cellular infiltration in the mucosa, and in severe cases in the submucosa. There is also desquamation of the lining epithelium, with an abundance of mucin-containing goblet cells. On the free surface is a certain amount of exudate made up of mucin, fibrin, and leukocytes (Adami and Nicholls).

Symptoms.—In mild trachea-bronchitis there are rarely any general symptoms. If the bronchi become more widely infected some general symptoms are always present, but are light and soon abate. There is some loss of appetite, coated tongue, weakness, pains in the limbs, chilliness and a little fever; often also herpes. Occasionally distinct chills occur. The fever seldom lasts beyond two or three days; if it persists it will be found to be due to some complication, usually bronchopneumonia.

The pulse rate is nearly always increased, and may, in people with irritable or diseased hearts, give discomfort, or even be of grave significance. The arteries of the large and middle-sized bronchi are not from the pulmonary, but from the aorta and internal mammary arteries, and the return blood is not to the left auricle, but in the veins of the general circulation; so that in bronchitis in the early stage heart disturbance is not due to obstruction of the lesser circulation. Probably the pulse disturbance is to be regarded as due chiefly to toxin acting on the heart and greater vessels, as in other infectious diseases. It is to be noted that not only in influenza bronchitis, but also in acute bronchitis of other

kinds that persists for weeks or months, a marked irritability and weakness of the heart may remain, which shows itself in arrhythmia and rapidity of pulse, and also in a general appearance of illness. The signs of a persistent cardiac insufficiency, especially in older people, may make its appearance and later become markedly increased after acute bronchitis.

The bloodvessels of the finer bronchi belong chiefly to the pulmonary circulation, therefore bronchiolitis has a marked effect on the pulmonary circulation, so that the right heart and pulmonary arteries are distended with blood. This obstruction to the pulmonary circulation is not so much due to the inflammation of the fine bronchi as to the obstruction to the entrance of air or the associated bronchopneumonia.

In deformed chests acute bronchitis is a serious disease; the small size and defective expansion of the lungs lead to dyspnoea and obstructed circulation, with any narrowing of the air passages. Even in the normal chest with sound lungs and heart, extension of inflammation to the fine bronchi always leads to dyspnoea. In many autopsies, especially in older people who in life showed no symptoms of insufficiency of the right heart, the wall of the right ventricle is remarkably thin; it may be streaked, and in many parts replaced by fatty tissues. So long as the lung *expands* fully, a very thin right ventricle wall will suffice to maintain a free pulmonary circulation. The inspiratory aspiration of the blood into the lungs, and its expiratory expression, will, with an intact valvular apparatus, efficiently promote the flow of blood from the right to the left ventricle. So soon as the expansion of the lungs suffers, as by rigidity or deformity of the chest, by emphysema, and by induration of the lungs, hypertrophy, and later dilatation of the right ventricle begin, even although the capillary area in the lungs is not narrowed.

Cough is a constant symptom; it is not only due to presence of secretion, but also, and chiefly, to the irritability of the inflamed mucous membrane. In chronic bronchial diseases, and especially in advanced pulmonary tuberculosis, large quantities of sputum may be expectorated by hawking only and without definite cough; in acute bronchitis the cough is more frequent and more violent than the slight quantity of secretion calls for. The *sputum* at the beginning is scant, mucoid, frothy, and almost transparent; it may be streaked with blood. It is never serous, as is secretion from the nose; there are no serous glands in the bronchi. After a few days it becomes opaque from the presence of pus corpuscles. The masses are separate and not confluent.

In the lightest cases of tracheobronchitis the infection does not extend beyond the largest bronchi; in these cases occasionally a sonorous rhonchus may be heard over both lungs; it is due to mucus at the tracheal bifurcation. If present in one lung only, it is produced in one of the large bronchi. Usually there are no changes either on auscultation or percussion, the cough and sputum being the only indication of the disease. When the infection extends to the medium size bronchi, the general symptoms are more marked; over the lungs are to be heard sonorous and sibilant rhonchi, varying in degree in different parts. As the secretion becomes more abundant, finer rales are heard over the back and front of the chest. The breathing is not altered, and the lung

area is unchanged. The breath sounds are normal. Rales of varying kinds may be heard all over the chest, showing the invasion of the finer bronchi. Here and there they disappear, while in surrounding parts breathing is normal. These silent areas may be altered by deep inspiration and cough; they are evidently due to obstruction of small bronchi.

In the adult, *capillary bronchitis* (bronchiolitis) is rare, but occurs oftener in children in whom immunity is probably less. It occurs in areas here and there also in older people, and in persons subject to chronic bronchitis and emphysema. From the more severe infections, as of influenza and measles, it may, however, occur even in vigorous adults.

If the entrance of air is not obstructed the lungs become distended, so that the thorax is expanded to its utmost and is only raised in inspiration. The diaphragm is depressed, and the lungs extend deeply in the chest. The percussion note is loud and deep; precordial dulness is reduced; the liver is depressed. After death the right heart is found greatly dilated and full of blood; the lung is distended with air and quite dry. The condition is one of marked obstruction to the pulmonary circulation. If the secretion of the larger bronchi is such as to impede the entrance of air, only the upper part of the chest becomes distended, while the lower is retracted and drawn in markedly in inspiration as in laryngeal obstruction. In the lower parts of the lungs areas of atelectasis occur, usually followed by infection, and bronchopneumonia results. In this group belongs the great majority of cases of capillary bronchitis. The rales of *capillary bronchitis* are widely distributed, fine and moist; the breathing sounds are often weakened, and may be absent over areas of the chest.

In primary cases the onset is sudden, as in pneumonia. The temperature may rise to 104° F. or more. Respiration becomes rapid, 60 or more in the minute. Each inspiratory act is short and quick, the expiratory longer and more difficult, and requiring the aid of the accessory muscles of respiration. Fine vesicular rales are abundant and widespread, somewhat larger, softer, and more vesicular than the fine crepitant rales which are caused by inflammation of the infundibulum and alveoli. The respiratory sounds are usually weak or absent in several areas of collapsed lobules. Even with a high temperature there may be a cold, clammy sweat. As the dyspnoea increases the expression becomes more anxious, the lips and cheeks show cyanosis, and the *alae nasi* dilate in inspiration. There is great restlessness, which gradually abates as the cyanosis deepens. In fact the whole picture is that of bronchopneumonia. Until the small pneumonic areas in such cases coalesce to form large masses of consolidation, the multiplicity of fine rales completely obscures the physical signs of pneumonia, yet the diagnosis may usually be made by the general symptoms which become much graver than those of uncomplicated bronchitis.

Diagnosis.—In the adult the diagnosis is seldom difficult or uncertain, yet cases are met with that baffle the most skillful. The difficulty is not so much in diagnosing bronchitis as in being certain that it is the primary and only affection, and not secondary to some other disease whose symptoms are latent or masked, as whooping cough, influenza,

typhoid fever, or acute tuberculosis. Much can be done to prevent error by careful bacteriological examination of the sputum. However, even the finding of pneumococci, streptococci, or influenza bacilli in the sputum does not necessarily exclude the existence of some latent disease, although it will furnish strong grounds for such exclusion.

A localized bronchitis is usually symptomatic; for example, bronchitis limited to the apex may be the first sign of pulmonary tuberculosis, that of both bases is usually due to hypostatic congestion, resulting from cardiac disease. Influenza also often causes localized bronchitis. Bronchitis of the larger tubes, especially in children, may be due to irritation from enlarged bronchial glands; in such cases the cough is generally of a violent, convulsive character. A similar cough may be caused by disease of the upper air passages, and by foreign bodies in the bronchi. In mitral stenosis the bronchi are very susceptible to catarrhal infection owing to the obstructed circulation; in such cases the sputum may contain some bright-red blood, often in large quantities, and the affection may be confounded with tuberculous disease.

Incipient pulmonary tuberculosis may simulate simple bronchitis. There is usually a history of gradual failure of health, yet it must not be overlooked that tuberculosis is not rare in stout, florid people, who are apparently in good health and complain of nothing but an irritating cough with scanty expectoration. No signs may be found on examination, or, at most, only a few evanescent, moist, or piping rales at the apex. A hasty diagnosis should not be made in such a case, as unnecessary anxiety may be excited and undue therapeutic measures undertaken. Careful observation is necessary, and if still in doubt a tuberculin test should be made.

Miliary tuberculosis is generally marked by a higher and more persistent fever, more prostration, and greater shortness of breath. It will not be amiss to repeat that the fullest investigation of the sputum, when present, affords, with few exceptions, the most certain basis for a diagnosis.

The diagnosis of *capillary bronchitis* is often very difficult. The dyspnoea, the auscultatory signs, the fever, and the signs of intoxication and asphyxia distinguish it from ordinary bronchitis. As already pointed out, it is probable that the lungs are affected in all cases and that the condition should, therefore, be regarded as bronchopneumonia.

Prognosis.—Except in the very young and in the aged, the bronchitis of the larger tubes is rarely fatal, but there is considerable uncertainty as to the duration of the attack and the completeness of recovery. By the profession as well as the public the affection is viewed with too much indifference, and to the want of care is often due the frequency with which slight catarrhal affections of the trachea and larger bronchi persist after acute bronchitis. Mild cases usually require ten days or two weeks, and severe ones, especially the streptococcus cases, three or four weeks to make a satisfactory recovery. Even after that, the recovery in many of them is incomplete and they are susceptible to recurrences of cough after slight chills. In the emphysematous, recovery is nearly always tedious, often requiring several months, especially in cold, damp climates.

A fatal termination scarcely ever occurs, except in young children and old people, or in patients suffering from such grave diseases as nephritis, heart disease, diabetes, chronic bronchitis, and emphysema; in these bronchopneumonia is a frequent and dangerous sequel. The signs of danger are the evidences that indicate failure of the right ventricle, as cyanosis, pulsation in the veins of the neck, visible cardiac impulse at the lower end of the sternum, great dyspnœa, short, ineffective cough, cold sweat, and a weak, rapid, irregular pulse. There is little hope of recovery in a case presenting such a symptom-group.

A severe attack of bronchitis in an infant may be fatal in a day; if less severe it may drag on for a week or more before death. In older children the duration is longer and the recoveries more frequent. The unfavorable signs are those that point to failing power in the respiratory, circulatory, and nervous systems, as dyspnœa, lessening in frequency and force of cough, and consequent cessation of expectoration, cyanosis, delirium, coma, and convulsions.

Bronchitis in the Aged.—Bronchitis is one of the commonest affections of old people and shows a remarkable tendency to extend to the smaller tubes. The affection in the aged and in children constitutes the condition designated by Sydenham "*Peripneumonia Notha*." The tendency to great exhaustion is the most characteristic feature of the disease in the aged; in other respects the symptoms do not indicate the gravity of the affection. There is usually no fever, the pulse is good, and the respiration only moderately quickened. Expectoration is easy as a rule, and the cough, therefore, not excessive. But there is a marked tendency to depression and drowsiness. The nights are restless, appetite is lost, but thirst is usually marked; hence the urine is copious and in the drowsy state is frequently passed unconsciously. The disease is most frequently due to a streptococcus infection, and if not early fatal generally passes into a chronic bronchitis.

Most cases terminate finally in bronchopneumonia, but this develops so insidiously, as a rule, that it may escape detection even by the most acute observer. Cough and expectoration often diminish, the temperature and respiration remain undisturbed, but the pulse grows weaker and more rapid as the vital powers fail. Owing to the rigidity of the chest wall usually little can be determined by physical examination, therefore, in many old people who have shown no symptoms but prostration with somnolency and feeble pulse, the morbid changes of unsuspected bronchopneumonia are found at the autopsy.

Prophylaxis.—Much can be done to prevent catarrhal affections by the adoption of a healthful manner of living. Next to good, well-prepared food, cleanliness is of the first consideration, cleanliness of air, as well as of person and surroundings. Air not being tangible, its purity does not appeal to the masses as do other forms of cleanliness. In the crusade against tuberculosis the necessity of fresh air has been so much insisted on that its importance in the maintenance of health, as well as in the treatment of other diseases, is in danger of being lost sight of. Next to a vigorous, outdoor life should be placed the daily cool bath, the temperature being graded according to the age and constitution of the

individual. The clothing, the bed, the sleeping-room, the avoidance of chill in dressing, and many apparently trivial matters should receive careful attention. All these considerations require attention, not only to keep the healthy well, but also to increase the resistance to recurrences of the attacks in those who have had bronchitis. Unhealthful occupations, especially those in which there is much dust and the air is impure, should be avoided. The dwelling-rooms should not be overheated, nor the air too dry. The clothing should be light, absorbent, and suitable for the season, but burdening with clothes in any season should be avoided. Coddling, as well as irrational exposure, like all extremes, is bad. In all cases the nasopharynx should receive appropriate treatment, if catarrhal processes or chronic thickening of the lining membrane be present, as this is so frequently the source of infection of the bronchi.

Treatment.—In the opinion of most people mild cases of bronchitis do not require any treatment, as they deem it but a slight ailment. They therefore seldom stop work or modify the routine of the daily life, too often with serious consequences.

As the affection is common and there is no specific treatment, it follows that many plans of treatment have been tried, rational and irrational. As in other diseases, the patient rather than the disease should be the object of treatment. As patients differ so much in vigor and constitution, it is not surprising that various and even opposite plans of management should often prove equally successful in attaining the object aimed at. No uniform course of treatment can be the best for all, so that each case should be considered on its own merits. Our aim is to secure arrest of the affection and the removal of its effects in the shortest possible time. It is probable that in many cases the attack can be arrested at the onset by confining to bed, and giving atropine, about gr. $\frac{1}{100}$ (0.0007 gm.) to arrest the secretion of the bronchial mucosa, and hexamethylenamine, gr. x (0.7 gm.), every two hours to disinfect the mucous membrane, by which it is partially excreted. Quinine may also have a beneficial influence.

Rest is of the first importance; all patients recover more quickly if kept to their rooms, and in well-marked cases the patient should be kept in bed during the acute stage. The clothing should be sufficient for warmth, but not burdensome. The temperature of the room is usually most agreeable at about 70°, and least likely to excite cough. The air should be pure and contain a moderate amount of moisture. Of late years a large and growing number of capable observers have advocated the free admission of cold, pure air to the patient with serious bronchitis or bronchopneumonia. Cold air is more dense than warm air, and therefore contains more oxygen per volume; it also stimulates respiration so that the inspirations are deeper and the blood therefore becomes better aerated. Cold air, however, especially if moist, may excite cough and dyspnea, probably by causing spasm of the bronchi; in such cases the admission of cold air is not desirable until the excessive irritability has been relieved. Long confinement to warm rooms is injudicious in all cases; if protection from cold and moisture is necessary a mild, dry climate should be sought.

As regards applications to the chest, the extremes of heat and cold, with all variations between, are used. The object of all of them is to lessen hyperemia and swelling of the bronchial mucous membrane, and thus remove or reduce the obstruction to the entrance of air. As none of these applications can have any direct influence on the vessels of the mucous membrane their influence must be reflex. Brunton has shown that cold applied to the surface causes blanching of the bronchial mucous membrane; but if the cold is continued too long the membrane soon becomes congested again. Heat possibly acts in a similar manner, although it may be that the action of both is due in part to the fact that they allay spasm of the bronchi. Both heat and cold often give effective relief, but cold has the advantage in that it is more easily applied, and that it excites deeper inspiration. Cold is most easily applied by using a *compress* of two to four layers of gauze, old linen or cotton, cut large enough to cover the whole chest; the compress is wrung out of cold water, applied closely so as to be in intimate contact with the surface of the chest and covered with a dry, thin flannel, to permit of evaporation. The coldness of the water and the frequency of changing the compress must be regulated according to the patient's strength and the urgency of the symptoms. The *cold, wet pack* is very useful for nervous patients. Cold douches and cold rubs are more stimulating and are therefore suitable for the vigorous. *Electric light, vapor, or Turkish baths* in the early stage of acute bronchitis do much good, especially if the perspiration be free.

Heat is usually applied by a poultice of linseed meal, with or without mustard. The poultice, to be effective, must be applied very hot, burning being prevented by a layer or two of flannel placed beneath it, and the whole covered with flannel, waxed paper, or rubber cloth to retain the heat as long as possible, and hold the poultice in close contact with the chest. The whole front of the chest should be covered with the poultice, which should be changed on cooling. It is difficult to accurately estimate the value of poulticing, but that the benefit derived from its use is much less than is generally supposed by the profession and public there is no doubt. Chief among the objections to its use is the great weight, a grave fault, as in serious cases the muscles of respiration are already overtaxed, and it is in these that the poultice is most needed.

Free perspiration, especially at the beginning, often moderates and not rarely aborts an attack. A full warm bath, at a temperature of 100° to 105°, for ten to fifteen minutes, is usually effective. The patient should be at once placed in a warm bed, and diaphoresis encouraged by giving hot drinks. Hot bottles may be put around the patient, who is covered by blankets.

Inhalations. These are probably next in importance, especially in acute cases. Even the vapor from hot water is grateful and soothing to the irritable bronchial mucous membrane. Its efficiency can be increased by adding various volatile and antiseptic remedies, either sedative or stimulant, such as eucalyptol, thymol, oleum pini sylvestris, or compound tincture of benzoin, of any one of which about a dram is to be put into a pint of water at 150°. A dram or more of light carbonate

of magnesia is usually added. Camphor, of which menthol is most commonly used, is an excellent addition, about 2 grains being added to a pint. Carbolic acid is also useful. Several ingredients may be effectively combined, as follows: *Oleum pini sylvestris*, oil of eucalyptus, of each 15 drops (1 cc.); menthol, 5 grains (0.3 gm.); light carbonate of magnesia, 10 grains (0.7 gm.); compound tincture of benzoin, 1 oz. (30 cc.). Of this combination a teaspoonful is to be put into a pint of hot water and the vapor inhaled.

Atomizers and nebulizers are useful, chiefly for the application of spray to the upper air passages, although after their use tests have shown the presence of the medicine in the pulmonary alveoli and in cavities. Simple saline solutions are much used; they quiet the cough and render secretion more liquid. They have more effect in the early stages. In severe cases they should be used frequently, every two or three hours for a few minutes at a time. After the acute stage is passed, menthol gr. v to x (0.3 to 0.6 gm.), camphor gr. x to xv (0.6 to 1 gm.), liquid paraffin $\overline{5j}$ (30 cc.), are useful when the trachea and larger bronchi are affected.

Internal Remedies. In simple colds, confinement to the room, a little opiate, and a hot drink usually suffice to give relief. In more severe forms with fever and aching pains, *quinine sulphate*, 7 to 10 grains (0.5 to 0.65 gm.) per day, if given at the beginning of the affection and during the following three or four days, may quickly cut short the general symptoms and lessen the duration. If quinine fails to give relief, antipyrine or phenacetine may be tried; they usually relieve the general symptoms.

In the early stage of the disease the vascular depressants are much used, as they cause the vessels to dilate and thus increase the secretion, especially the serous portion of it. They are the so-called sedative expectorants, such as tartarated antimony, ipecacuanha, apomorphine, and pilocarpine. Of these, pilocarpine is the most effective; apomorphine is next, but is used more often; opium may be added to this group, but it is, as a rule, given to allay cough by diminishing the irritability of the mucous membrane. The dose of these depressants should be small and frequently repeated to maintain their effect. Of pilocarpine, from gr. $\frac{1}{125}$ to $\frac{1}{60}$ (0.0005 to 0.001 gm.) three to four times a day should be sufficient for an adult; West gives gr. $\frac{1}{8}$ (0.008 gm.) three times a day. Apomorphine gr. $\frac{1}{10}$ (0.006 gm.), gradually increased to gr. $\frac{1}{5}$ (0.013 gm.), will usually cause copious bronchial secretion. If given early, tincture of aconite, $\overline{m\j}$ (0.06 cc.) every fifteen to twenty minutes for about eight doses, will generally cause free perspiration and a fall in the temperature. It is quite safe for persons of ordinarily robust health. The addition to any of these drugs of liquor ammonii acetatis, $\overline{5iij}$ to iv (12 to 16 cc.), and spirit of nitrous ether, $\overline{3ss}$ to j (2 to 4 cc.), increases their efficacy by stimulating diaphoresis. These remedies are being used with less and less frequency, as they are more or less nauseating; hot teas and salines usually answer the purpose, for which they are given equally as well. They are only of use while the secretion is tenacious and scanty, and they should not be continued longer than a few days.

Small doses of morphine, gr. $\frac{1}{60}$ to $\frac{1}{50}$ (0.001 to 0.0013 gm.), may in the aged suffice to relieve the excess of cough and at the same time improve the general condition. The derivatives of morphia, especially heroin, gr. $\frac{1}{30}$ to $\frac{1}{16}$ (0.002 to 0.004 gm.), and codein, gr. $\frac{1}{8}$ to $\frac{1}{4}$ (0.008 to 0.016 gm.), may prove quite as effective and be less likely to cause undue depression. The labored breathing, the frequent cough, and the excess of carbonic acid in the blood produce such a sense of great fatigue and desire to sleep that a sedative to give sleep is often begged for; to yield to the solicitation may take away the last chance of recovery. If the dyspnoea is less urgent, one or two hours' sleep may be induced by one of the bromides, gr. x to xv (0.6 to 1 gm.), with a small dose of chloral, gr. v to x (0.3 to 0.6 gm.); but the sleep should be short, and coughing and expectoration encouraged when the patient awakens.

If the cough becomes ineffective and mucus accumulates to such an extent that suffocation threatens, an emetic must be given, such as gr. xx (1.3 gm.) of ipecacuanha. Apomorphine is more rapid and certain and rarely causes depression. A dose of gr. $\frac{1}{5}$ (0.013 gm.) by the mouth or gr. $\frac{1}{10}$ (0.006 gm.) subcutaneously usually suffices in the adult; for young children, about gr. $\frac{1}{25}$ (0.0027 gm.). The act of vomiting usually forces much of the mucus out of the bronchi with great relief to the breathing.

Bleeding was once regularly resorted to in bronchitis as in other inflammatory diseases, but its indiscriminate use doing much damage, it fell into disrepute. Of late the practice has been somewhat revived, and with gratifying results when judiciously used. "It does most good in robust, full-blooded adults in acute attacks" (West), but bronchitis in such patients rarely needs such heroic measures. It is with signs of overstrain of the right ventricle, such as dyspnoea, commencing cyanosis, rising pulse, etc., that bleeding is called for. It produces gratifying results if it lessens the distension of the right ventricle so as to enable it to contract fully, raise the pressure and force the blood through the pulmonary capillaries. To be effective the bleeding should be free, as the relief of the distension of the right ventricle depends on the suddenness with which the volume of blood flowing to it is reduced. Children, the aged, and the very feeble of all ages do not bear bleeding well; the advisability of resorting to it in others is to be estimated by the state of the right ventricle. Ten to fifteen ounces should be removed; saline solution can be given subcutaneously after the heart has been relieved, if the loss of blood is considered a serious matter.

Whether practical benefit results from the inhalation of *oxygen* in severe bronchitis is doubtful. That it should be of benefit seems reasonable; but it often fails to do good, and may even add to the patient's distress by proving irksome to him. If its administration is begun before severe dyspnoea has set in, while the patient can still with ease inhale the gas, it is probable that he will be able to continue its use at a later stage, when the breathing has become much more distressed. It may prove stimulating and less irritating if passed through warm absolute alcohol.

If the heart shows signs of failure, caffeine may prove an efficient

cardiac stimulant. The pure alkaloid is the most reliable; gr. iij to v or more (0.2 to 0.4 gm.), rendered soluble by the addition of benzoate or salicylate of sodium, may be given hypodermically every three hours. Digitaline may be added. Pituitary extract is probably the most useful of all cardiac stimulants. A capsule of it (1 cc.) should be injected into the muscle of any part. The effect may last one or even two days.

Alcohol, especially in old people, may do much good in quieting restlessness and calming a weak, irritable heart. Six or seven ounces of brandy or whisky may be required in the twenty-four hours.

The nursing of bronchitis is of great importance, especially in severe cases, as relapses are very liable to occur. The patient should be carefully guarded against chilling, and the air not permitted to become impure. The more severe the attack, the more frequently should the patient be awakened at night so that cough may be excited to insure the expulsion of secretion and prevent dangerous accumulation in the bronchi.

The drinking of liquids freely is desirable, in order, by stimulating the action of the skin and kidneys, first, to reduce the congestion of the bronchial mucous membrane, and, secondly, to remove toxic substances which might act as irritants. In the young, the aged, and the feeble, extreme care is needed to maintain strength and yet not overtax the powers of digestion. Liquid foods are usually all they can digest. The diet should be regulated according to the patient's appetite and digestion. In adults of ordinary vigor, if there is no desire for food, none is required for the first day or two.

Autogenous *vaccines* in cases of slow convalescence and of recurrence may effect a complete cure. The vaccine should contain the chief organisms present in the sputum.

Chronic Bronchitis.—**Etiology.**—Repeated attacks of acute or subacute tracheobronchitis may in time become persistent, the inflammation extending slowly to the deeper structures of the bronchi. The majority of cases, however, begin insidiously, and are due to persistent injury of the mucous membrane by such inhaled particles as dust particles and gases, or to passive pulmonary congestion, whether from cardiac inefficiency, or chronic affections of the lungs, or both together. The disease is therefore of frequent occurrence among stone-cutters, weavers, grinders, bakers, millers, miners, etc. Hoffmann regards alcoholism as the most important and most frequent cause of chronic bronchitis among all classes. Alcohol is partly excreted by the bronchial mucous membrane on which it acts injuriously, as well as on the muscular coat and the bloodvessels, and, it may be added, on the vascular system generally.

Chronic bronchitis is frequent in emphysema, in valvular affections of the heart which disturb the pulmonary circulation, in chronic nephritis, and from long-continued inhalation of irritant substances as gases and dust.

Pathology.—In *chronic bronchitis* the condition varies with the degree and duration of the inflammation. The milder and more recent cases differ little from the acute except that the inflammation penetrates more deeply and the secretion is more purulent. The mucous membrane is œdematous, reddish or dark, owing to the full dilated bloodvessels; it

is infiltrated and covered with mucopurulent secretion. All the bronchial walls are infected, and the seat of a greater or less degree of leukocytic infiltration. In the advanced cases the mucous membrane is irregularly thickened, partly owing to infiltration, and partly to the formation of new fibrous tissue which may extend into the peribronchial structure, and lead in time to fibrosis of the lung. Long-continued inflammation may lead to destructive ulceration of all the coats of the bronchus, which dilates, forming a bronchiectatic cavity with profuse purulent secretion; or the inflammatory products may become absorbed together with all the structures of the bronchial wall—mucous membrane, muscular coat and cartilages—leaving a thin, dilated bronchus (Adami and Nicholls).

Symptoms.—In general, they are those of bronchitis without the acute symptoms; in fact, it is often difficult to differentiate between mild, recurring attacks of acute bronchitis and the chronic variety. In many of these cases of recurring attacks, some inflammation persists between the attacks, in the trachea and larger bronchi, with, at most, only slight, occasional cough and little expectoration, most frequently in the morning. Many of the cases of *winter cough*, the most common form of chronic bronchitis, have a history of preceding recurrent attacks of the acute disease, but many of them develop gradually and without acute symptoms. The trachea and large bronchi only are affected and therefore no physical signs are evident. People past middle life are most frequently affected, especially those who are rather stout and are given to free indulgence in food and drink. The bronchial affection begins as a troublesome morning cough which is often replaced by wheezing; the cough persists until the night's secretion has been expelled, after which there is usually relief for the remainder of the day.

The *sputum* may be scanty, but it is often copious. It is mucopurulent, thick, and yellow, and may sink in water like that of chronic pulmonary tuberculosis.

If there is little or no emphysema, the breathing is normal; the general health is good and quite equal to the active duties of life. In a few years in most cases the relief in summer grows shorter and less complete and the cough in winter more severe, and the general health begins to fail. When the disease is of a more severe type it affects the smaller tubes early; all the symptoms are more marked. The cough is more severe, may be paroxysmal, and at times with more or less wheezing.

Dyspnœa in some degree is never absent; it is caused by the emphysema and interstitial pulmonary fibrosis which always develop. It becomes paroxysmal, and labored, if the secretion is abundant and adhesive.

Slight causes are apt to excite exacerbations of cough, and necessitate confinement to the house or room for a few days. In the intervals, however, the general health is good. In more severe and advanced cases the symptoms are much worse. Cough is often most troublesome at night and expectoration may be profuse. There are frequent recurrences of fever, due to fresh attacks of bronchitis or bronchopneumonia, or to other than disease of the respiratory organs. Emaciation, loss of strength, night-sweats, loss of appetite, and disturbed digestion are

usually present. The right ventricle fails, as shown by cyanosis, enlargement of the liver, distension of veins, clubbing of the fingers, and even well-marked pulmonary osteo-arthritis. Later, cardiac dropsy supervenes, the urine becomes scanty and albuminous, weakness becomes so great that the bronchial secretion cannot be expelled, and death takes place from failure of the vital powers. Besides the ordinary mucopurulent bronchitis, which is much the most common, there are three other clinical varieties deserving of special notice.

1. *Dry Catarrh* (Catarrhe sec of Laennec).—This is of rather rare occurrence. Laennec considered it very frequent, but he probably included the cases of winter cough already described. Apart from winter cough it is an uncommon affection. From time to time in the mucopurulent variety there may be cessation of secretion and then the symptoms are those of dry catarrh.

Dyspnoea is marked, and there is severe paroxysmal coughing with a little sputum, which is found to contain numerous small, pearl-like masses of tough mucus, with pus cells and blood corpuscles in its meshes. Charcot-Leyden crystals and Curschmann's spirals are often present. The cough often causes acute tearing pain referred to a spot at the attachment of the abdominal muscles to the lower margin of the thorax. Fothergill attributed the pain to the violence of the cough causing the tearing of muscle fibres from their attachments to the periosteum.

On *auscultation* there are many piping rales with hissing sounds; there may also be moist and creaking rales. Later the dyspnoea becomes continuous, owing chiefly to the emphysema, which nearly always develops; the course is marked by paroxysms like those of asthma, in which the wheezing and piping rales are marked all over the chest.

2. *The Serous Form of Catarrh*.—This, also first described by Laennec, is rare. It is distinguished by the expectoration of profuse, mucoserous, translucent, colorless sputum, which separates into an upper frothy layer, and a lower clear one like egg albumen or gum arabic mixed with water. The rarity of this affection is shown by the few cases reported in recent years, and the variety in the descriptions given of it by different writers. West describes an acute and a chronic form. "As a primary disease the *acute* is very rare; but in a mild form it is not very uncommon in many pulmonary affections." It may appear as a suffocative catarrh, and in children prove rapidly fatal.

The *chronic form* is commonly preceded by ordinary catarrh, and once established, it is usually intermittent. During the twenty-four hours several pints may be expectorated, often in copious quantities at short intervals. It may persist for years without change in character, and the patient's general condition be little affected; some cases are probably of the nature of a nervous hypersecretion. It may occur as a terminal phenomenon in acute tuberculosis, acute pneumonia, pleuritic effusion, cardiac disease, etc. Occasionally a profuse serous discharge occurs in cases of thoracic aneurism or mediastinal tumor. It may occur after aspiration of a pleural effusion and give rise to extreme dyspnoea, which may prove fatal from filling of the bronchi with serous fluid. The patient is drowned in his own secretion.

3. *Purulent Bronchitis* (Bronchoblennorrhœa).—Purulent bronchitis is the third form described; it is more or less marked in the final stage of all cases of chronic bronchitis, but there may be a marked purulent sputum from the first, a pint or more being expectorated in the twenty-four hours, as if a large cavity or an empyema had ruptured into a bronchus. The pus may become offensive but the odor soon abates; the odor is less marked than in putrid bronchitis. Purulent bronchitis may become converted into the putrid variety, however, especially if bronchiectasis develops. As a rule the patients lose flesh early, but the course of the malady is usually chronic. West has seen an acute form develop in the course of typhoid fever. A pint or more of sputum was expectorated in twenty-four hours; the cases were not fatal, the symptoms disappearing with convalescence.

Diagnosis.—In all cases of *chronic bronchitis* of whatever kind, the most important question is whether the condition is not a variety of, or at least a combination with, tuberculosis. If the sputum is fully, and, if necessary repeatedly, examined, it is remarkable how often the tubercle bacillus is found, even although the course has been fever free and all the indications point to ordinary chronic bronchitis. The sputum, however, may not contain bacilli, and emphysema may obscure the signs of local changes. Disease in any part of the lungs, especially the apex, without apparent cause, is presumptive evidence of tuberculous infection. In doubtful cases a tuberculin test will generally give positive evidence if tuberculosis exists.

Prognosis.—In the young the outlook is often hopeful, even when they are emphysematous and subject to attacks of asthma. Many improve as they grow older, and in time the symptoms may completely disappear. After middle life there are few recoveries, but many are able to lead comfortable, useful lives, and may attain advanced age, unless carried off by some intercurrent affection. In the severer cases various complications are certain to arise in time. Of the complications general *emphysema*, the most common, is rarely absent. It increases the dyspnoea as well as the liability to recrudescences of the bronchitis. *Interstitial fibrosis* of the lungs is common, and may lead to the gradual development of bronchiectasis. Much weight should be attached to the state of the cardiovascular system, as in the late stages the chief danger is from failure of the right ventricle.

Treatment.—It is of the first importance to avoid a cold, wet, and foggy climate; but it is in just such climates that the affection is most frequent, and, unfortunately, most sufferers are unable to seek a better one. A mild sea air is usually most beneficial in the winter, such as Nassau, Bermuda, Jamaica, Cuba, Florida, and Southern California in America; in Europe, the Mediterranean Coast, Sicily, Madeira, the Canary Islands, and the Isle of Wight. Some patients, especially those with tuberculous tendencies, do better in a dry, warm climate, such as Mexico, New Mexico, Arizona, and Colorado; and in the East the higher parts of Georgia and the Carolinas. Not rarely it will be found best to try moist and dry climates alternately.

In the summer months a more bracing climate will usually be found

most beneficial if a continuous outdoor life is led, especially in the forest districts or on the plains. In Canada, Muskoka, the forests of Northern Ontario and Quebec, the plains of the Northwest, the foot-hills of the Rocky Mountains, and many parts of British Columbia offer admirable opportunities for such a life. In the United States, the New England and the Pacific Coast States are the best. Experience has proved that all these parts afford excellent resorts for tuberculous patients, and they should be equally favorable for chronic bronchitis, but as yet little consideration has been given to the subject. In time it will probably be shown that in chronic bronchitis, as in tuberculosis, the all-important matter in the treatment is not the mild climate, but the outdoor life, care being taken to keep the body and limbs warm so as to prevent congestion of the bronchial mucous membrane. Even in the Yukon, long-standing cases of chronic bronchitis have quickly recovered.

If the patient is unable to leave home, no effort should be spared in improving the general condition. This will necessitate as much outdoor life as possible. The clothing should be light but warm so as to prevent chilling of any part. Mouth breathing should be avoided, and, if necessary, a respirator worn to warm the air.

The closest attention should be given to the functions of excretory organs, so as to counteract the strong tendency that exists in many of these cases to the accumulation of waste products in the blood. The diet should be ample for the needs of the patient, but excess should be avoided. Cod-liver oil, if it does not disturb appetite or digestion, benefits many, especially those of spare habit.

Autogenous vaccines should prove of much benefit in all cases, if given before the bronchi have undergone organic changes the cure should be complete.

The *cough* is usually more frequent in the morning, less so on lying down at night, and not rare during the night; it is often relieved by giving bicarbonate of soda in warm milk. At Brompton Hospital a combination of sodium bicarbonate, gr. xv (1 gm.); sodium chloride, gr. v (0.3 gm.); spirit of chloroform, ℥v (0.3 cc.), in anise-water, added to an equal quantity of warm water, is the usual combination administered. If the sputum is scanty and viscid, ammonium carbonate and potassium iodide, of each gr. iij (0.2 gm.), may be added.

Hydrotherapeutic measures suitable to the individual case are regarded by the German physicians as the most effective of all methods of treatment. These measures are best carried out at a properly equipped institution, but many of them can be utilized at home. Full warm baths of long duration repeated from time to time are efficient aids in lessening secretion and making it more easily expelled. They will effectually replace much of the expectorant medication.

If acute attacks occur, they are to be treated as indicated in acute bronchitis. The more depressing remedies are, however, rarely advisable and should not be given to the feeble or the old. If the secretion is viscid and scanty, the use of alkaline fluids in a fine atomizer, better the nebulizer, may give much relief. If not effective, inhalations of the vapor of hot water to which have been added one or more of the volatile

measures, especially hydrotherapeutic ones, will go far to obviate the necessity for internal medication.

Sulphur and arsenical thermal waters have been found useful in both the dry and purulent forms of chronic bronchitis and are much resorted to in Europe.

These measures usually suffice to control the cough if it is due to the secretion rather than to excessive irritability of the mucous membrane. In the latter case something having more sedative effect will be needed. The addition of 15 to 20 drops (1 to 1.4 cc.) of chloroform to the inhalation may sufficiently moderate the cough; if not, one of the bromides may be added to the warm alkaline mixture already specified. If this is insufficient, heroin or codein will have to be given until the cough is sufficiently controlled, due caution being taken, however, that necessary cough is not interfered with; or paregoric, a time-honored remedy, may serve the purpose better, as the camphor stimulates the circulation of the debilitated and the aged. Whisky at bedtime, especially in the aged, often serves the double purpose of quieting the cough and causing refreshing sleep.

General treatment is required as indicated, in each individual case. Iron, quinine, strychnine, cod-liver oil, glycerophosphates, etc., may aid in improving the general health, and, insofar as they do so, in lessening bronchial secretion. The digestive organs should receive careful attention. Owing to the general weakness and the loss of muscular tone and fat, gastropnoxis is apt to occur, followed by gastric atony with its train of symptoms resulting from protracted retention of the contents of the stomach. The diet should therefore be suited to the digestive powers of the individual as determined by a careful investigation.

The treatment of *asthmatic attacks* occurring in the course of chronic bronchitis will depend on their character. The more purely spasmodic they are, the more effectively will morphia hypodermically relieve them, but it is a dangerous remedy if there is much secretion. In the latter cases "the drugs of greatest value are potassium iodide, gr. viij to xv (0.6 to 1 gm.); extract of stramonium, gr. $\frac{1}{4}$ (0.016 gm.), and the ethereal extract of lobelia, \mathfrak{m} 20 (1.3 cc.), in combination with stimulant expectorants, such as carbonate of ammonia, gr. iij to v (0.2 to 0.4 gm.), or ether" (Fowler). As there is general venous fulness a saline purgative sufficient to cause a free action of the bowels will be of much benefit.

In those in whom there is damage of the heart, the greatest dependence must be placed on cardiac stimulants and tonics. Pituuitary extract or digitalis should be taken in short courses from time to time. Exercise in the open air, but not beyond the powers of the patient, so as not to overstrain the heart, is probably the best of all cardiac tonics. Respiratory gymnastics are of much benefit; as are also daily cold baths, provided they are followed by a feeling of exhilaration. Similar treatment is called for in the corpulent, in whom also the bronchitis is due to defective circulation.

In alcoholics, the failure of circulation is the chief cause of bronchitis, but toxemia is also an important one. In their treatment, in addition

to improving the vigor of the heart's action, it is necessary that alcoholic drinks be much reduced or stopped, and the digestion and excretion restored as far as possible to a healthy state.

In the advanced stage of chronic bronchitis with dyspnoea and cyanosis from failure of the right ventricle, temporary relief may follow a rapid venesection, ten ounces or more of blood being taken in a full stream in order to rapidly lower the distension of the right ventricle. Cardiac and general stimulants, such as pituitary extract, strychnine, digitalis, caffeine, ether, and alcohol, should be given according to the individual needs. Inhalations of oxygen may give much relief.

If respiration is impeded by the accumulation of secretion in the bronchi and suffocation is threatening, an emetic may afford temporary relief through the act of vomiting expelling the secretion. In the debilitated condition of these patients it is a dangerous remedy; it should not be resorted to in the more feeble, lest it produce fatal depression. As in all these cases there is labored expiration due to emphysema, compression of the chest during expiration by the hands applied over the axillary regions should be made several times a day to assist in expelling the secretion, as recommended by Ewart. This should be carried out while the patient lies prone with the shoulders hanging over the side of the bed or couch. The *posture* during the night already described, if assumed, should prevent this accumulation of secretion.

Respiratory gymnastics of any form are valuable in chronic bronchitis. They should be carried out in air that is pure and free from dust, as in the forests and at the sea-shore. They are best carried out without apparatus, as they can be taken at any time and in any convenient place. Deep inspirations followed by long and forced expirations will prove useful exercises to anyone who patiently perseveres in their use.

Secondary Bronchitis.—Bronchitis is a frequent complication of a variety of diseased conditions. As a rule the symptoms and physical signs do not differ from those ordinarily met with in primary bronchial affections. It is not necessary therefore to do more than point out the relationships of these various diseases to the etiology of the bronchitis and their influence on its course and treatment:

1. **Bronchitis in the Course of Febrile Diseases.**—In *measles* some degree of bronchitis is always present, so that it may rightly be considered an essential part of the disease. As the smaller tubes are usually affected, it is from the bronchitis with its complications, especially bronchopneumonia, that the chief source of danger arises in many cases.

In *typhoid fever* slight bronchitis is of such frequent occurrence in the initial stage of the disease that it may be regarded as caused by the typhoid toxin. By some this initial bronchitis has been attributed to the early localization of the typhoid bacillus in the bronchial mucous membrane. Late in the disease, when the heart becomes weak and toxemia pronounced, bronchitis may be the occasion of much anxiety; it is caused partly by the toxemia and partly by the defective circulation. The symptoms in such a case are due to hypostatic congestion as well as to the bronchitis. There is much danger of bronchopneumonia from extension of the inflammation.

As a sequel to *whooping-cough*, bronchitis with collapse of lobules is frequent; it may cause a paroxysmal cough similar to the original disease. The bronchitis of *influenza* is of special importance owing to its frequency of occurrence and its influence on the mortality of the influenza. The mucous membrane of the trachea and bronchi shows the usual changes of acute catarrh. The secretion, especially of the smaller tubes, at first is viscid and often blood-stained. The inflammation is very prone to extend to the deeper structures of the bronchial wall; this accounts for the frequency with which influenzal bronchitis is followed by bronchiectasis.

The occurrence of bronchitis varies in different epidemics in influenza, as well as in different persons in the same epidemic. It has been a more frequent symptom of late years. It may occur early, beginning as a coryza. Cough is usually frequent, short, dry, and very distressing. It is very persistent and difficult to relieve. The expectoration may be very scanty throughout, or it may become free as the attack advances. It is often adhesive and scanty at first, but may become mucopurulent and copious later. The severity of the general symptoms will depend upon the extent and size of the bronchi affected. If the inflammation extends to the capillary tubes the respiratory symptoms will be severe and it will be difficult to determine that bronchopneumonia has not developed. It may be confined to any part of the lung, and, therefore, difficult to distinguish from tuberculosis.

Treatment.—This does not differ from that of other forms of acute bronchitis. There should be due appreciation of the gravity of the affection, of its long duration in all marked cases, and its liability to terminate in chronic bronchitis and bronchiectasis.

2. Bronchitis of Gout.—This is of the chronic recurrent form affecting the larger tubes. The etiological relationship is so clear that many gouty persons recognize it themselves and often take advantage of the warning to forestall an arthritic attack. The bronchitis usually precedes, but may follow, an attack or occur during its course. The bronchitis often occurs as a morning cough usually quite out of proportion to the expectoration, which consists of a small quantity of yellow secretion. Piping rales may be present and the breathing is often “wheezing.” As the gouty age is after middle life there is usually more or less emphysema.

Fowler describes another form of gouty bronchitis met with in middle-aged persons and characterized by sudden onset and more severe symptoms, with marked cardiac disturbance. There may be marked dyspnoea and cough, and the presence of fine, bubbling, and crackling rales, chiefly at the bases of the lungs; fever may be slight or absent. These symptoms may be followed by an acute arthritic attack, or they may subside under treatment without further manifestations of gout.

In persons subject to gout, chronic interstitial nephritis is liable to develop; and then similar attacks of bronchitis may occur from the pulmonary congestion and oedema caused by the cardiac changes associated with the renal disease.

3. Bronchitis in Heart Disease.—This is of great importance, both as a sign of the existence of the affection of the heart and of the impending

failure of its function. Three varieties have been distinguished: the bronchitis of mitral affections, of aortic affections, and a form occurring in cases showing myocardial, arteriosclerotic, and valvular lesions.

Of these, the bronchitis in *mitral insufficiency* is the one most often seen and most important. It generally affects both lungs and is chiefly due to hypostatic congestion. It is characterized by small, moist rales which are marked at the base, and diminish rapidly from below upward. There is ordinarily a small quantity of effusion into the lower part of the pleural cavities. It is a bronchitis of progressive character, slow in development, and without sudden accessions. It causes gradually increasing dyspnœa exaggerated by slight exercise, in marked contrast to the nocturnal dyspnœa of asthma with emphysema. The cough is variable but fatiguing even when not severe. The sputum is mucopurulent and varies in quantity; in it are found the so-called *cardiac insufficiency cells*. These are large cells containing reddish or rust-colored pigment from blood; in health these cells contain black pigment. They probably come from the alveoli, as they resemble the epithelium normally found there. They are found almost constantly and in such numbers in hypostatic congestion from heart disease that they have been regarded as quite characteristic, but incorrectly, as they occur also in the sputum of bronchitis and asthma. They are characteristic only of hypostasis in which the cells become full of pigments.

In *mitral stenosis* there are frequently recurring attacks of bronchitis in many cases. At first these attacks are slight and the expectoration consists of frothy mucus; later it often becomes tinged with blood. If the right ventricle becomes well hypertrophied so as to maintain a high degree of tension in the pulmonary vessels, free hemoptysis is frequent and may prove fatal. In such a case known to be due to mitral stenosis at autopsy the pulmonary arteries were found the seat of marked atheromatous degeneration, and greatly dilated even to their smallest branches. The right ventricle was very greatly hypertrophied but not dilated. In the *diagnosis* of the bronchitis of mitral stenosis the error is often made of mistaking it for pulmonary tuberculosis, chiefly on account of the hemorrhagic sputum, but also because of the anemia, absence of cyanosis, and late dropsy of mitral stenosis. A careful examination should prevent the mistake.

Bronchitis occurring in affections of the myocardium and of the aortic orifice and in the course of arteriosclerosis has been described. It is probably due, in the early stage, to renal disease, and later to cardiac failure, which is in reality relative mitral insufficiency. Huchard's *bronchite à répétition de la myocardiite scléreuse* is apparently of the same nature.

Treatment.—This should have for its first object the improvement of the circulation, as the chief danger is from failure of the heart. The patient should therefore be placed at rest, and the diet should be dry in order to add as little as possible to the volume of the blood, which is already too great. Heart tonics and stimulants, especially digitalis, will be required to strengthen the heart and increase excretion by the kidneys; purgatives will be of use chiefly by lessening the volume of the

blood. In conditions of weak and irregular heart with sleeplessness, morphia hypodermically is usually the only effective heart tonic, and its use is seldom attended with danger in this form of bronchitis. Potassium iodide may do much good by acting on the bronchial mucous membrane, rendering the expectoration easy and quieting the cough, and at the same time acting favorably on the myocardium. If there is œdema, diuretin or theocin may be effective in strengthening the heart and stimulating the kidneys. The diet should be salt-free.

4. **Bronchitis in Renal Disease.**—Three forms of bronchitis in renal disease have been described by Lasègue: (a) A simple and common form attended by migratory and fugitive bronchopulmonary œdema. The cough is slight, but dyspnoea of greater or less degree requires treatment. This dyspnoea is paroxysmal, but is not increased by movement, and is worse at night than in the day, often attaining a severity sufficient to cause orthopnoea—the so-called renal asthma. On careful auscultation over one or several areas, crepitant rales are audible; these areas are not confined to any part, but may be found in the upper lobe, at the base, or in the axillary region. They never occupy a whole lobe. The rales are fleeting and may change from place to place during prolonged auscultation; rarely they persist in the same place for several days. If localized at the apex they simulate tuberculosis. This form occurs without fever, and is of short duration, but may recur with great facility. It may occur at the commencement of albuminuria or at any time during the course of the disease in a latent case.

(b) The second form constitutes what is properly called *albuminuric bronchitis*. It occurs in chronic cases, develops suddenly, and may attain great intensity. The dyspnoea is intermittent and paroxysms are frequent. The cough is frequent, increased during the paroxysms, and accompanied by mucopurulent expectoration, often with blood intimately diffused or in filaments. This form occurs without fever, disappears after a certain time, and is liable to recur.

(c) The third form gives the impression of a veritable *bronchopneumonia*. The onset is often brusque, with fever. The cough is severe and frequent, and increases for several days. The expectoration is abundant and sometimes sanguinolent. The oppression is marked and continuous, with paroxysms. On auscultation there are generalized bronchitic rales; after these disappear areas of persistent crepitation are still left. The affection begins in the large and descends to the small tubes, thus showing that the persistent areas are pneumonic. In the final stage of chronic nephritis, when the patient is nearly moribund, a diffuse congestion and œdema often occur, with large, moist rales, due to the stasis of the mucus in the bronchi, and caused chiefly, if not wholly, by cardiac failure.

The Causation of the Bronchitis of Cardiac and Albuminuric Affections.—The causes in these two affections are closely allied. Passive congestion and œdema affect the bases of the lungs; they are the mechanical result of the enfeeblement of the heart that is the rule in cardiac cases, and is frequent in chronic nephritis.

The variable and fleeting congestions and œdemas are evidently due

to *vasomotor disturbances*. In chronic nephritis they are doubtless caused by toxins acting on the vasomotor nerves of the bronchi, or on the centres in the medulla. In the cardiac cases they are apparently of analogous origin, the poison exciting them being partly due to renal insufficiency, and partly to the carbonic acid in the blood due to mitral insufficiency.

"*Renal asthma*" is a term of very uncertain significance and applied to dyspnoea arising from a variety of causes. Occasionally in chronic nephritis there are paroxysms of dyspnoea that cannot be distinguished from true asthma and are probably due to the same cause. But the term renal asthma is not confined to these cases, but applied to all kinds of dyspnoea occurring in chronic nephritis in which sudden attacks of difficult breathing, especially at night, are quite common. These attacks are often caused by uremic poisoning, but probably more frequently by the disturbed circulation in the lungs and nervous system arising from heart failure. Bronchitis in some degree always coexists and aggravates the dyspnoea in both the uremic and cardiac cases.

The treatment is such as is best for the renal affection: milk diet if there is no oedema, otherwise dry diet; free action of the bowels; potassium iodide in suitable cases. These means usually ameliorate the bronchitis as well as act favorably on the renal affection. Dry cupping of the chest may do much good, many cups being applied to all parts of the chest, front and back. They may be repeated two or three times a day. Sedatives are often injurious. As cardiac affections usually coexist with the renal, both conditions should be considered in the treatment.

TUBERCULOSIS OF THE TRACHEA AND BRONCHI

Tuberculous infection of the trachea and bronchi is generally regarded as secondary to pulmonary tuberculosis and is not usually treated of as a separate disease. In the trachea and at least the larger bronchi the disease is a rare one except near the end of life, and even then it is far from frequent. This relative immunity is accounted for by the following conditions: (1) The trachea and bronchi form simple, smooth, open tubes, whose walls never come into contact nor present any irregular cavities in which the sputum can lodge and be compressed. (2) Their surfaces are protected by a layer of mucus which is being constantly moved upward by the strong ciliary motion of the epithelium, carrying along with it all foreign substances that have lodged on it. For this reason the surface never presents any deposits of carbon particles,* even although the respired air be laden with them. (3) The ciliated epithelium is highly irritable. Catarrhal inflammation and a heavy coating of mucus lessen their activity and hence reduce their protective power (Kraft). (4) The tracheal and bronchial mucous membrane is highly sensitive and excites reflex cough when irritated by foreign substances.

For these reasons primary tuberculosis of the tracheal and bronchial mucous membrane is very rare; and in the pulmonary affection it usually escapes because the sputum is hurried along so rapidly as to prevent infection of the healthy membrane, and render it infrequent even in

the abraded areas, which are usually protected by a thick layer of mucus. Toward the end of life irritability is lessened and the sputum, travelling more slowly, destroys more frequently the less resistant epithelium, so that the bacilli often find an entrance. The posterior walls are injected most frequently because in the bedridden they are the more exposed.

The tuberculosis of children is essentially a tuberculosis of the small bronchi. This is indicated by the frequency of the disease in the bronchial glands and by the rarity of hemoptysis, of chronic, circumscribed, apical consolidation, and of cavity formation. The strong tendency to tuberculous bronchopneumonia is further evidence of the bronchial invasion.

Two processes have been demonstrated pathologically, viz., tuberculosis of the bronchi and tuberculous or caseous bronchitis. Clinically, neither one of them is known, both being obscured by the more important pulmonary symptoms which always coexist. Rindfleisch regards the terminals of the bronchioles as the point of most frequent infection, but probably somewhat larger branches are also not rarely infected. The bronchial wall becomes infiltrated with small cells, causing considerable thickening, and the area of infiltration is soon converted into a yellowish-white, well-defined mass. The epithelium becomes destroyed early, and the mass, unless the process becomes arrested and absorption takes place, degenerates and is discharged into the bronchus, leaving a small, caseous ulcer. The tendency of the process then is to penetrate more deeply and excite peribronchial inflammation and later involve the lung tissue itself.

Leprosy also occurs in the bronchi, and presents changes similar to those of tuberculosis bronchitis.

SYPHILIS OF THE TRACHEA AND BRONCHI

Nothing definite is known of the occurrence of the secondary lesions of syphilis in the trachea and bronchi, either as mucous plaques or condylomatous masses. The laryngoscope has revealed red, slightly elevated patches like the macular and papular eruptions on the skin, which have rapidly disappeared under treatment. A few instances of syphilitic tumors have also been observed to disappear under treatment. These lesions doubtless occur likewise in the bronchi and give rise to some degree of irritation with symptoms of bronchitis.

Tertiary lesions are associated frequently with disease in the larynx, also with affections of the lungs, liver, etc. The lesions are most frequent near the bifurcation, occurring both in the trachea and bronchi. The gummata vary in size from that of a pinhead to a walnut. One or several may be present, or the deposit may be diffuse in the mucous membrane. It infiltrates all the coats of the bronchus, even the cartilages becoming affected. The swelling rarely causes sufficient stenosis to disturb respiration, the symptoms being those of subacute or chronic tracheitis and bronchitis, with more or less profuse purulent expectoration, which is occasionally blood-stained, especially in the ulcerative

stage. The ulceration extends as deeply as the infiltration, so that healing may be followed by extensive scarring that may cause much deformity. The gummatous infiltration may be circumscribed and lead to ulcers and scars, or diffuse and cause widespread destruction of the mucous membrane and diffuse perichondritis. The first condition is found chiefly in the larger bronchi and often causes hemoptysis; the second follows the course of the bronchi and invades the lungs, causing considerable cirrhotic change. The two forms, however, are not sharply separated but merge into each other.

Symptoms.—The symptoms are those of ordinary bronchitis. In some cases there is an unusual quantity of blood in the sputum. Gradually the symptoms of stenosis develop with increasing expectoration, which affords some relief when copious and bloody, but the symptoms grow worse when the sputum becomes scanty and only mucopurulent. In some cases instead of the symptoms of stenosis those of hectic fever occur, and the condition then simulates pulmonary tuberculosis, hence the name "phthisis syphilitica." If secondary tuberculous infection takes place it may completely overshadow the original disease. Various complications, especially bronchiectasis and bronchopneumonia, are quite frequent.

Diagnosis.—This is not difficult if there is a clear history and the throat shows the usual signs of the disease. In the absence of these guides, the diagnosis is not easy, tuberculosis being especially difficult to differentiate. Tubercle bacilli if present in the sputum do not necessarily exclude syphilis, as tuberculosis may occur as a secondary infection. All the diseases causing stenosis will have to be considered before arriving at a diagnosis of a syphilitic lesion.

Treatment.—This should be vigorous, mercury and potassium iodide being given freely. They should be given even in developed stenosis, the object being to remove all recent exudate about the scar. Salvarsan should prove as effective as in syphilis elsewhere. The stenosis may be explored by the bronchoscope and, when possible, appropriate surgical treatment adopted.

FIBRINOUS OR PLASTIC BRONCHITIS (PSEUDOMEMBRANOUS BRONCHITIS)

This affection is characterized by the occurrence of a coagulable bronchial exudate from which are formed cylindrical or solid casts of the bronchial ramifications. It is a rare affection. Up to 1869 Lebert was able to find only 44 undoubted cases in the literature. In 1889 West found 54 more cases, and Bettmann in the literature from 1869 to 1902 found 145 cases (including West's), making, with Lebert's list, 189 in all. Since then up to May, 1907, there have been 12 undoubted cases recorded in the *Index Medicus*. To these the writer can add 3 unreported cases: 1 from the Museum of the Medical Department of the University of Toronto, 1 of extensive casts associated with hemoptysis occurring in the practice of W. J. Wilson, of Toronto, and 1 under the care of T. McKenzie.

The occurrence of casts was known to Hippocrates, Galen, and other ancient authors.

Etiology.—This affection may occur at any age, but is probably rarest in old people. Like bronchitis, it is most common in cold, damp climates, and therefore in the cold seasons of the year. In *diphtheria* it may occur as a sequel to disease of the fauces and larynx, especially the latter. The reported cases, however, are not numerous probably because the complication has often been regarded as a matter of course, and therefore not calling for a special report. In 220 autopsies, Councilman, Mallory, and Pearce found definite membranous deposit in the bronchi in 42 subjects. Although usually secondary, a primary fibrinous bronchitis may doubtless also be caused by the Klebs-Loeffler bacillus.

Fibrinous bronchitis occurs in association with a great variety of diseases, so various, in fact, that the association appears accidental. The largest number has occurred in persons affected with pulmonary tuberculosis and heart disease. It has been met with in the course of the various infectious diseases, such as pneumonia, measles, scarlatina, erysipelas, typhoid fever, variola, rheumatic fever, and influenza. A few cases have occurred in association with asthma and some with pulmonary oedema following thoracentesis. Inhalation of irritant fumes and gases, as smoke, steam, and ammonia, has been the cause in some cases. A few cases have been reported as occurring in connection with severe pemphigus affecting the skin and the mucous membranes of the mouth and throat; the affection has been regarded as essentially a pemphigus of the bronchi.

An apparent relation of fibrinous bronchitis to menstruation has been observed. In a case of Graves' disease a fibrinous exudate occurred during the administration of potassium iodide. Then there are some cases for which no cause can be assigned, primary idiopathic cases. These may occur in robust, previously healthy people. With the exception of diphtheria and pneumonia, we are not certain that the affections with which the occurrence of the fibrinous exudate is associated bear a causative and not an accidental relationship; the association would seem to be merely a coincidence.

Pathology.—Little is known as to the pathology of fibrinous bronchitis. It seems certain that a variety of agencies may cause a membranous exudate. There is no doubt that the pneumococcus and diphtheria bacillus may cause membranous exudate in the bronchi as elsewhere, but whether other microorganisms cause it also is uncertain. It is also uncertain whether all cases are due to bacteria, as no microorganisms can be found in some specimens. The exudate may form solid casts of the bronchi, or hollow cylinders, or both may be present in the same case. The casts from the small bronchi are probably always solid and from the larger ones hollow. The inclusion of air bubbles may give the casts a beaded appearance. The exudate may be produced in a few bronchi only, or occur in several areas in one or both lungs. Nearly all the casts in museums have been coughed up, few being found in the bronchi at autopsy.

Casts vary in length from an inch or so up to six or seven inches,

with branches corresponding to the divisions of the bronchi from which they are expelled. They are pearly gray or white in color, the larger firm and the smaller softer in consistence. The larger are laminated, the inner layers showing foldings due to the forcing of the older layers farther and farther from the bronchial wall and toward the centre of the tube, by the successive deposits on the mucous membrane beneath them. The terminal casts are spiral in form, and the sputum may contain Curschmann's spirals, Charcot-Leyden crystals, and eosinophilic cells, indicating a condition of the mucous membrane similar to that in asthma. The casts usually consist chiefly of fibrin; some are of mucus, but many are found of both in varying proportions. In the meshes of the laminae are found epithelium, Charcot-Leyden crystals, fat globules, and, in the outer layers, sometimes blood corpuscles.

Marfan describes three classes of casts: (1) In pneumonia and acute, idiopathic, fibrinous bronchitis the casts are yellowish. They are solid, but show imprisoned air bubbles. They consist of leukocytes and fibrin, and are designated leukocyto-fibrinous casts. (2) In diphtheritic bronchitis the casts are white, opaque, and often hollow. They are composed chiefly of fibrin and degenerated epithelial cells—*fibrino-epithelial casts*. (3) In chronic pseudomembranous bronchitis the casts are white, transparent, and often hollow; they are *mucos-albuminous*, *fibrinous*, or *fatty*.

The condition of the bronchi is uncertain. The epithelium must be destroyed to some extent, but the destruction may be limited to small areas.

Symptoms.—Dyspnoea, cough, and the expectoration of casts are the essential symptoms, the presence of casts in the sputum being the characteristic one. The following case in the practice of T. McKenzie gives a good illustration of the symptoms:

The patient was a female, aged twenty-seven years. The bronchial attack for which she first sought advice in November, 1905, began in the late summer. She had a dry, irritating cough, with little sputum, and at times coughed severely for several days, when she vomited some white substance. During the consultation she had a severe paroxysm of coughing and brought up a cast, receiving it into her handkerchief without being aware of its existence until it was shown to her. The bronchitis continued until February, and during this time she had four marked paroxysms, in one of which she coughed up almost a complete cast of the bronchi of the lower lobe of the left lung, one considerably larger than the one shown in the illustration, Fig. 55. In the intervals between the paroxysms the sputum consisted of a moderate quantity of milky fluid containing small white masses of membrane. All the paroxysms in the morning began with chilly and shivering sensations, and in the afternoons there were hot flushes and chilly feelings. Her throat was dry, the cough was irritating, and increased by the slightest exertion. After a day or two casts would be brought up and she would improve and promise a speedy recovery. But a slight cough continued and the physical signs over the lower part of the left lung persisted. There was slight but varying dulness, most marked before and diminish-

ing after the expulsion of the casts. Coarse crepitation was audible, beginning about the middle and continuing to the end of inspiration, apparently due to the separation of the casts; it resembled a coarse, exaggerated crepitation of pneumonia. The temperature varied from subnormal to 100° ; the pulse was rapid, especially during the paroxysms;

FIG. 55



Cast from a case of fibrinous bronchitis.

sleep was disturbed by the cough and soreness across the middle of the chest. There has been no recurrence for some years, and her health is quite restored.

Diagnosis.—In typical cases there is no difficulty in diagnosis; the casts by themselves leave no room for doubt. From *asthma* there may be much difficulty in diagnosis, and in all doubtful cases the sputum should be carefully searched for pellets and masses of rolled-up casts. A small *foreign body* in a bronchus causes similar attacks, but the history and relapses of

fibrinous bronchitis will prevent error. *Diphtheria* is to be excluded by the bacteriology and the absence of membrane in the fauces and of laryngeal symptoms. In *pneumonia*, as in diphtheria, casts may also occur, but the history and physical signs usually leave no room for doubt. In *bronchitis* the occurrence of an attack of dyspnoea and the absence of respiratory sounds over an area of lung, with but slight impairment of the percussion note, might be considered sufficient for a diagnosis, but to make it certain the sputum should be carefully searched for casts.

Prognosis.—A fatal result is rare in an uncomplicated case. In Fagge's case the loosened cast became lodged at the tracheal bifurcation and caused death by asphyxia. In the rare form in which acute attacks follow one another in rapid succession, death may occur during a paroxysm, usually within one or two weeks from the onset of the disease. Extensive deposits in the bronchi doubtless occur in such cases. The marked tendency to recurrence is to be borne in mind. The intervals between attacks may be short or long, and liability to them may continue for many years.

Treatment.—The value of any treatment in a disease that runs such an uncertain course as fibrinous bronchitis is difficult to estimate, as any relief following recourse to it may be the natural course of the disease, uninfluenced by the treatment. Potassium iodide is the only drug regarded as of material value by English and American writers. It should be given in full doses. Mercurials seem to have little influence

on the affection, even when given freely. Water vapor, especially that from lime-water, is highly valued by German observers. Arsenic has been followed by striking results in some cases, but there may be a recurrence. Creosote in vapor, or in the nebulizer, continuously inhaled, may prove of much value. Intratracheal injections of oil, plain or medicated, have been used. Ewart reports a favorable result in a case in which creosoted oil (1 in 20) was dropped at intervals through a tracheotomy tube. Injections may be given by Mendel's method or without difficulty by injection through the glottis.

The general management of these cases should be guided by the principles on which the treatment of simple bronchitis is carried out. In dyspnoea, the inhalation of oxygen may give relief and aid in sustaining life until the cast is expelled, but in most cases, fresh cold air will probably be found more agreeable as well as more efficacious. The associated conditions, of which cardiac disease and pulmonary tuberculosis are the most frequent, require suitable treatment. Claisse obtained notable improvement by the use of Marmorek's antistreptococcic serum. In rebellious cases change of climate is advisable. The seaside, if not otherwise contra-indicated, may be tried.

FETID OR PUTRID BRONCHITIS (GANGRENOUS BRONCHITIS)

Fetid or putrid bronchitis is a rare affection. It is not a definite disease, but only a peculiar form of decomposition which may occur in the secretion in any disease of the lungs or bronchi; it may be a passing phenomenon in any form of chronic bronchitis.

Etiology.—Fetid bronchitis is always a secondary affection which only develops in bronchi previously altered by *acute or chronic bronchitis*, *bronchiectasis*, *chronic tuberculosis*, or by *foreign bodies* in the bronchi. It is probable, therefore, that the microorganisms which cause the putrefaction are able to develop only on mucous membrane whose epithelium has already been injured or destroyed. Those most liable to the affection are such as those whose vitality is depressed by privation, alcoholism, and malnutrition from any cause. The definite microorganisms that give rise to the decomposition have not been determined; many are found in the secretion and probably several may be able under varying conditions to cause it. Bacteriology has not, as yet, added much to our knowledge of the condition.

The *Oidium albicans* has apparently been the cause in some cases, the decomposition following exposure to thrush infection. Cases are reported in which *Leptothrix pulmonalis* and *Bacterium termo* have been found in abundance in the secretion. From the sputum of a case of fetid bronchitis, four varieties of staphylococcus, a diplococcus, and a bacillus were isolated, and possibly each of them was able to cause decomposition. *Bacillus coli communis* is said by some to be the usual microbe of gangrenous bronchitis, and a germ called the *Bacillus putridus splendens* has been described as pathogenic (Bernabei).

Pathology.—The morbid changes are few and not constant. The medium-sized and small bronchi are chiefly affected. The diseased

bronchial wall is reddish, wine-colored, or pale gray. The epithelium is cast off, and on scraping the surface with a scalpel a soft, fetid pulp is exposed. In many places the wall of the bronchus is destroyed and the process extends to the peribronchial tissue; it may lead to the formation of actual gangrenous cavities. Thus putrid bronchitis is not only an almost constant complication, but also a frequent cause of bronchial dilatation.

The process may terminate (1) in complete recovery or in bronchiectasis; (2) in fatal chronic septicemia or in abscess of the brain; (3) in extensive gangrene of the lung.

Symptoms.—The characteristic symptom is the horrible, gangrenous odor of the patient's breath and sputum; it often permeates the room and even the whole house. The sputum is remarkable for its abundance, especially if there is bronchiectasis, amounting in many cases to several ounces in twenty-four hours. It is mucopurulent in character, and ordinarily separates into three layers. The *upper layer* forms the greater part of the sputum; it is frothy and greenish. It consists of mucus, holding in its meshes many pus and epithelial cells. The upper part contains many air bubbles, and from the lower surface many brownish flakes hang down into the fluid below. The *second layer* consists of dirty, greenish, thin fluid, incorrectly called serum. The *third layer* is formed of sediment of various kinds: detritus, fat drops, and peculiar, horribly offensive pellets known as Dittrich's plugs. These plugs vary in size from a microscopic point up to a bean; they contain fat needles, leptothrix, leucin, tyrosin, and fine granules from degenerated cells. These plugs were first described by Dittrich; Traube regarded them as characteristic.

Cough is frequent, but not severe, as the sputum is brought up in large quantity with ease. *Fever* is present in many cases, and, being septic, is a serious symptom. It is probably due to the absorption of putrefactive products.

The disease usually begins rather suddenly and is essentially paroxysmal. In strong persons it may disappear after one or many weeks, leaving the patient uninjured. It recurs not infrequently. In severer cases septic symptoms rapidly develop, often beginning with chills. Signs of prostration soon follow, and the patient passes into a typhoid state. Cough and expectoration cease and death in collapse follows.

In some cases complications occur, such as ulceration and gangrene of the lung, and bronchopneumonia, with diffuse bronchitis. In others, metastatic fetid abscesses form in various organs. The disease presents a very varied history, and the descriptions of the earlier writers varied according to the kind of cases seen. Thus Trousseau describes a relatively mild class, while Traube, Sée, and Andral give the details of cases of great severity which were usually rapidly fatal. Sée proposed the name of septic bronchitis for such cases.

Diagnosis.—The difficulty consists in excluding other affections giving rise to fetid expectoration. It is usually an easy matter to exclude the condition in which the fetor is due to disease above the larynx, that is, in the nose, mouth, or pharynx. When the cause lies below the

larynx, however, it may be impossible to be certain that the fetid discharge does not come from bronchiectasis, a gangrenous cavity in the lung, or a gangrenous abscess in the mediastinum or elsewhere in the thorax. In fact, a putrid bronchitis apart from one of these conditions is very rare, so rare that its existence has been questioned, although a few cases, with autopsy, have been reported. It is scarcely possible, however, in any case to exclude bronchiectasis with certainty.

In *gangrene* of the lung, the onset is more sudden, hemoptysis is usually of frequent recurrence, and shreds of pulmonary tissue will probably be found in the sputum; elastic fibres are not often found, as they are rapidly dissolved in the gangrenous fluid.

Fetid expectoration may result from the rupture into a bronchus of an empyema, of an abscess of the vertebræ, the lung itself, or the liver; or of a subdiaphragmatic abscess due to appendicitis or other abdominal disease. In all these conditions symptoms usually develop suddenly without preceding bronchitis, and the source of the pus may be evident on examination. On the other hand, a diagnosis is often impossible; even a postmortem examination may leave it in doubt.

Treatment.—To maintain the best possible general condition and correct the fetor usually sums up the utmost that can be done. For the former, pure outdoor air is of the first importance; then rest or exercise such as each case requires, sufficient nourishment, and the necessary tonic and stimulating remedies accomplish all that we are able to do for the general health. For the fetor, inhalations of antiseptic vapors are usually the most effective remedies. The best deodorant is probably creosote given by inhalation. Inhalations of turpentine have long been resorted to and are often useful. Both remedies may be given internally. West regards musk, a grain in a pill, or an equivalent of the tincture, given three times a day, as the most efficacious remedy. Intratracheal injections of antiseptic remedies should be effective. Autogenous vaccines should be of much benefit.

BRONCHIECTASIS

The first description of this affection was given by Laennec, whose attention was directed to it in 1808 by his assistant Cayol, then a student. Laennec, however, does not seem at first to have appreciated the importance of the condition, and it was not until 1825 that his first description of it was published.

Etiology.—Bronchiectasis occurs partly as the result of an increased pressure acting on the bronchial wall, and partly as the result of a change in the texture and condition of the bronchial wall, as well as the surrounding lung tissue. The bronchi are always infected early, pneumococci and influenza bacilli probably being the most frequent infecting organisms. The infection gradually invades the whole thickness of the wall of the bronchi and peribronchial tissue. The diseased condition of the bronchi renders them less resistant to pressure, and therefore the more easily dilated by internal pressure or external traction.

Congenital bronchiectasis is met with, but is rare. After birth the disease occurs at all ages. It may be of gradual formation, or develop after acute infections, pneumonia, and pleurisy. In chronic cases the history may indicate only a probable onset of the disease. By the *status praesens* it can usually be determined whether the bronchial dilatation is diffuse affecting both lungs or confined to a small bronchial area, also whether the dilated bronchi lie in air-containing, or infiltrated, or in atrophied lung tissue.

Most cases of circumscribed bronchiectasis originate in pneumonia and pleurisy, so that the surrounding lung tissue is more or less shrunken. A section of such lung shows in the affected area a great many dilated bronchi in the fibrosed tissue. By the shrinking of this tissue the bronchi are deformed, in places narrowed, in others widened into cylindrical or saccular dilatations. The fibrosed area usually extends to the pleura, which becomes fibrosed and adherent to the chest wall. In diffuse bronchiectasis the adhesion to the chest wall not only prevents collapse of the affected bronchi, but increases their dilatation and holds their lumina gaping widely. Longitudinal sections of such a tube show an irregular pouching of the lumen between still intact circular bands of muscular and elastic tissue.

The wall of the dilated bronchus is always greatly altered; the peribronchial tissue is thickened, and usually markedly anthracotic. The mucous glands, the elastic fibres, the smooth muscles and cartilages, have become atrophic in the proliferating connective tissue. The mucous membrane is markedly congested, and usually infiltrated with leukocytes which wander into the lumen. The epithelium is irregular, in part cubical or even flat. Often epithelium is quite absent, and the bronchial walls become converted into granulation tissue which grows into the lumen in the form of small wart-like masses or ridges. In such cases the mucous membrane is destroyed and the bronchial tube converted into an ulcerating purulent canal. Such a bronchial wall is usually rich in thin-walled, distended bloodvessels, the rupture of which may give rise to profuse hemorrhage.

These changes in the wall of the bronchus, including the atrophy of the circular muscular and elastic coats, and the formation of the thick newly-formed surrounding fibrous tissue, make difficult the discharge of purulent secretion, which, therefore, stagnating, affords most favorable conditions for the growth of bacteria. In many cases the secretion becomes foul and may act destructively on the wall of the bronchus and the lung tissue. In such cases necrosis of the bronchial wall and offensive gangrene of the lung may result.

Circumscribed bronchiectasis occurs very often as a result of a *pneumonia*, which does not resolve but terminates in chronic induration. If the fibrosis affects only a small part of lung and the pleura is not adherent to the chest wall, the section of lung is drawn inward and the neighboring vicariously inflated lung section overlies and conceals the contracted part. On section one finds embedded in the cicatricial, hard mass a number of widely dilated bronchi lying close together. If, however, the cicatricial induration affects a greater mass, as a half or whole

PLATE XVI



Bronchiectasis. (Carswell.)

lobe, and if this is firmly adherent to the chest wall, preventing much shrinking of the indurated lung, a widespread and marked bronchiectasis will be found. The irregularly dilated, open bronchi, some cylindrical, some saccular, are embedded in a dense, strong, anthracotic connective tissue, and between the broad fibrous bands are found only scant remains of air-containing alveoli.

Chronic pneumonia may occur at all ages, but especially in children in whom it most frequently follows the bronchopneumonia of measles, whooping-cough, and influenza. Such pneumonia is usually atypical, rarely lobar. If a careful history leads to the diagnosis of circumscribed bronchiectasis, one may conclude in the majority of cases that there has been, perhaps many years before, an unresolved pneumonia with bronchitis, which was of long standing, with cough, which has never completely, or only after long continuance, disappeared.

Large *pleuritic effusions* are, in rare cases, followed by bronchiectasis. In such cases, after absorption, the portion of lung that has been long compressed does not again expand, the chest sinks in, and gradually the picture of bronchiectasis develops. In other cases the lung expands and no changes occur in its structure. After operation for empyema, the usual result is that the compressed lung expands to the normal. These varying results may be due to the occurrence of chronic inflammation in the compressed lung and that granulation tissue forms in the alveoli. Then in some cases the fibrous changes in the pleura may be followed by the extension from the pleura of interlobular strands of connective tissue, which, by their subsequent contraction, cause the ectasia of the bronchi.

Obstruction of a bronchus always causes dilatation of the peripheral parts of the tube. The obstruction may be by pressure, as from an aneurism or a mediastinal tumor, or from a foreign body in the bronchus or a cicatrix following syphilitic or tuberculous ulceration in the bronchus.

Cavities in the apices of lungs in phthisical cases are probably rarely bronchiectatic, but are cavities whose contents have been completely expelled leaving the cavity in free communication with a bronchus. It is conceivable that such cavities in markedly fibrosed lung tissue might be produced by the traction of the new connective tissue, but the bronchial walls are usually destroyed by tuberculous ulceration before the fibrosis has become fully formed. In most cases the structure of the cavity wall is formed of new connective tissue in either mode of formation, and would therefore not be a ground for differentiation.

The dilatations of the bronchi are due to (1) weakness of the wall of the tube; (2) distension of the tube from within; (3) traction upon the tubes from without. *Weakness* of the wall of the tube may be congenital. From whatever cause the wall may be so weak as to yield to the pressure of the contained air in straining or coughing. The weakness is usually the result of changes due to inflammation, especially chronic. *Distension* of the tubes from pressure within occurs in coughing, singing, straining, obstruction to escape of inspired air, and accumulation of secretion. Permanent distension of the tube soon leads to alteration in

the structure of the wall, which renders it less resistant, and it probably always becomes altered and further weakened by inflammation due to infection. *Traction* upon the tubes from without by changes in the lung and pleura is the most important cause.

Symptoms.—Paroxysmal cough and copious, purulent expectoration, often offensive, are the chief symptoms of bronchiectasis and without which a diagnosis is not possible. They occur most commonly on rising in the morning and on lying down at night; that is, change of position, if the cavities are full, causes dislodgement of secretion, and this excites the cough and expectoration. The dilated, diseased bronchi have lost their normal sensibility to such a degree that contact of secretion does not excite cough, and it is not until the accumulated secretion is brought into contact with the more healthy mucous membrane by movement or change of position that cough results, usually with the expectoration of large quantities of purulent secretion, as much as 25 to 30 ounces (700 to 900 cc.) being expelled in twenty-four hours.

The *sputum* is chiefly purulent; it is usually yellowish and has little adhesiveness. The stagnant, bronchial secretion becomes early infected by air-borne microorganisms of all kinds, including those which cause putrid decomposition. Both the breath and the sputum of the patients therefore usually become offensive, often extremely so. After standing some hours the sputum usually settles into two or, more often, three layers: the lowest one of thick, purulent material containing various kinds of granular debris, and forming an opaque, gray mass; over this a thin, turbid fluid; and if there is a third one, an upper, thin, frothy, brownish layer. In the lower, dense layer there are to be found pus cells, granular detritus, many microorganisms, and Traube's or Dittrich's plugs, which consist of fetid, soft, grayish-yellow bodies formed in the smaller bronchi from the pus, detritus, crystals, etc. Blood in the sputum is a late, but not infrequent, symptom. It is generally small in quantity and mixed with the secretion; but the bleeding may be profuse and repeated; it may even be fatal.

Fever may be absent throughout the whole course of the affection. In most cases, however, the course is marked from time to time by exacerbations of two or three weeks' duration, during which there are irregular elevation of temperature, increase of cough and expectoration, sweats, loss of appetite, etc. These attacks are probably due to fresh infections of the bronchi, the occurrence of new areas of broncho-pneumonia, and to absorption of septic material from the decomposing bronchial secretion. In cases in which there is marked venous stasis from cardiac weakness the temperature is, as a rule, subnormal.

Clubbing of the fingers is of frequent occurrence, and is important as a sign of bronchiectasis. The toes may become similarly affected. In more advanced cases similar changes may occur also in the other phalanges, in the metacarpal bones, in the bones of the wrist and forearm, leg, etc., until finally all the peculiar changes of pulmonary osteo-arthropathy are presented.

Lardaceous or amyloid changes are prone to occur late in the disease, diarrhoea and albuminuria are then often met with.

Physical Signs.—Bronchiectasis may be secondary to such a great number of diseases, and such a variety of morbid changes may develop in its course, that there may be the greatest variation in the physical signs. The signs are those of the associated conditions rather than of the bronchial dilatation. The chest may be enlarged and emphysematous, or, from fibrosis of the lung, it may be markedly retracted, and the heart displaced. The percussion note will vary according to the degree of dilatation, its proximity to the surface, the condition of the surrounding pulmonary tissue, and the thickness of the overlying pleura. If a large dilatation lie near the surface, the percussion note will be dull while the cavity is full of secretion, but will become tympanitic as the secretion is expelled and the cavity fills with air. Normal resonance immediately surrounding the seat of a cavity differentiates a dilatation from a tuberculous cavity, as the note is always dull in the vicinity of the latter. A cavity stationary in size points to bronchiectasis, while, as Stokes pointed out, an increasing excavation is preceded by consolidation and is peculiar to tuberculosis.

Auscultation.—In bronchiectasis with emphysema the respiratory sounds are vesicular with a tubular quality, but not cavernous. The sounds may be wavy, both in inspiration and expiration. When there is fibrosis around the dilatation, which is usual in the saccular variety, the vesicular breathing is lost and the sounds are definitely cavernous, usually with more or less "gurgling." Bronchophony and pectoriloquy may be marked. Adventitious sounds are present in great variety. In the absence of fibrosis there are soft rales, both large and small; if the lung is indurated they are higher pitched and crackling, or, more usually, coarse and metallic. They appear and disappear as the secretion in the tubes increases or lessens. Associated bronchial and pulmonary diseases produce a variety of rales which may obscure the signs of dilatation.

Complications.—The cause of death is often a complication. Severe hemoptysis, acute pneumonia, and bronchopneumonia are the most frequent. Gangrene of the lung in the neighborhood of the dilatation may occur and lead to a fatal termination. The diagnosis of such a complication is very difficult, as the odor and appearance of the sputum are similar in both affections. If, on microscopic examination, masses of pulmonary tissue are found, the existence of gangrene would be established. A bronchiectatic cavity near the surface of the lung may rupture into the pleural cavity which was not obliterated by adhesion; empyema or pyopneumothorax will follow, and either is usually fatal.

Pyemia is of frequent occurrence. In mild cases it may cause general malaise, with aching pains; in more severe infection various local infections may occur, such as abscess of the liver or kidneys, suppuration of joints, ulcerative endocarditis, and septic infection of the serous cavities. The most frequent of these metastatic infections is *in the brain*, causing *abscess*.

In many cases death results from cardiac failure due partly to general weakness, but chiefly to obstruction to the pulmonary circulation caused by the fibrosis of the lungs.

Diagnosis. This is only possible if the dilated bronchus produces abundant purulent secretion; it may be over many years, even decades. The mucous membrane of the cavity is so far destroyed that there is little mucus in the sputum, which is made up of purulent, granular debris and liquid, and separates into characteristic layers on standing. The varying signs from time to time, as the cavity becomes full and empty, and the fetor usually suffice for a diagnosis. Tuberculosis, chronic bronchitis, pulmonary gangrene, and a circumscribed empyema have to be differentiated.

Prognosis.—The disease is incurable, but may last for several decades. Notwithstanding the cough and expectoration the sufferer may be able to pursue his occupation. Yet he is liable to many accidents, of which secondary inflammation of the lung and pleura is the most important. Gangrene of the bronchus and the lung, and also lung abscess, are among the gravest, yet not rare complications. Hemoptysis is an occasional cause of death, as is also cerebral abscess.

Treatment. As our efforts to cure the dilatations are as yet ineffectual, we are reduced to the necessity of endeavoring to lessen the secretion and to keeping it as nearly aseptic as possible. The best means of accomplishing these objects is to have the patient live in absolutely pure air; this aids also in improving the general health. He must avoid crowded rooms because the air in them becomes impure. The greatest care must be taken to prevent inflammatory processes of any kind, even the slightest catarrh of the respiratory tract. In the attempt to render the secretion aseptic, use has long been made of inhalations of creosote, turpentine, carbolic acid, menthol, etc. These remedies have also been given internally. These methods of treatment are laborious, and have been only moderately successful. However success in several cases has resulted from the continuous inhalation of coal-tar creosote and the intralaryngeal injections of solutions of menthol, guaiacol, iodoform, creosote, etc., in olive oil, aided by the "postural" method. These remedies in sterilized oil have also been used as subcutaneous injections.

In the absence of any contra-indication, the patient should make systematic efforts at stated intervals to empty the cavities by assuming such positions, as the "knee-chest," the Trendelenburg, or, better, with the chest over the side of the bed and down as near as possible to the floor, to favor the discharge of secretion by gravity. By emptying the cavity by such "postural" assistance he is relieved, to a certain extent, of toxic effects, and the cavity is the better prepared for the vapor or fluid that may be applied to it.

The protracted inhalation of creosote vapor was first suggested by Chaplin.¹ The object is to excite sufficient coughing to force out all secretion from the bronchi, and to secure efficient disinfection by the prolonged inhalation of the strong vapor of creosote. In order to properly use the vapor, a small air-tight room should be set apart for the purpose, all openings about the doors and windows being packed with

¹ *British Medical Journal*, 1895, i, 1371.

cotton-wool. In the centre of the room, on a pedestal, a spirit lamp is placed, and over it a flat, open dish is fixed into which a sufficient quantity of creosote is poured. The usual amount varies from 15 to 30 drops. On lighting the lamp the fumes begin to rise and soon fill the room. At first only gentle heat is applied, the patient sitting in the room and inhaling the fumes. Later, the fumes can be inhaled with greater ease, and stronger heat may be applied, so as to fill the room with dense fumes in which objects can scarcely be distinguished. If the patient can bear it, he may sit stooping over the dish and inhale the vapor as it rises. As the vapor is strongly irritant to the eyes and nose, they require to be protected. This can be done by covering the eyes with two watch-glasses framed in adhesive plaster, and plugging the nostrils with absorbent cotton. With such protection the patient can stand an inhalation with comparative ease that could not otherwise be endured. At first, from a few minutes to half an hour is sufficiently long for an inhalation; later, it may be borne for one or two hours.

The effect of the inhalation is to excite violent paroxysms of coughing and cause the expulsion of large quantities of secretion, even although much has been expelled just before the inhalation began. This residual secretion is usually horribly offensive from having lain long in the cavities. The sputum, at first profuse and fetid, becomes, in favorable cases, gradually lessened in quantity and the odor diminishes; in four or five weeks the quantity may be trifling and the odor slight. The respiratory capacity improves so that much greater exertion can be undertaken without dyspnoea. The patient's general condition grows better in every way; the temperature, if elevated, gradually becomes normal, and the pulse becomes stronger. The chest, on examination, shows evidences of empty cavities with few rales.

The method of treatment has the merit of being inexpensive and easy of application. Unfortunately, it is not uniformly successful. The inhalation of creosote from a nebulizer, operated by compressed air, should be equally effective, and would be less disagreeable and easily managed. This method was successfully adopted recently by W. Warner Jones in bronchiectasis following influenza in a man whom the writer referred to him for treatment.

Treatment by intratracheal injections has given satisfactory results. The following may be used:

Menthol	10 parts
Guaiacol	2 parts
Olive oil	88 parts

A dram of this is to be injected twice daily, care being taken to introduce the tip of the nozzle of the syringe beyond the vocal cords. This fluid often proves quite irritating and causes severe coughing. Iodoform emulsion, 2 to 10 per cent., is less irritating and is probably quite as effective.

Mendel¹ has improved on this method. He says that "if the tongue of the patient is protruded and held outside the mouth, and if he at the

¹ *Lancet*, 1905, ii, 133.

same time refrains from swallowing, the pharynx forms a funnel in which the inferior outlet is the glottis, as the orifice of the œsophageal tube is closed except during the act of swallowing, so that a small quantity of liquid projected against the wall of the pharynx runs down into the air passages." The liquid may be projected against the posterior wall of the pharynx, but it is more convenient and equally successful if the syringe is supported against the posterior faucial pillar and the fluid projected against the lateral pharyngeal wall, from which it runs around to the posterior wall and thence down through the larynx into the trachea. The tongue should be kept protruded a few seconds after the injection, so as to allow time for the fluid to flow through the larynx. He advises the use of non-irritating antiseptics, as eucalyptol, 5 to 10 per cent. The first injections should be weak to allow time for the patient to become accustomed to them.

The essential oil in the fluid begins to evaporate as soon as it reaches the trachea and bronchi, and the vapor stimulates inspiration, causing greater expansion of the lungs. At first the increased expansion lasts only an hour or two, but the time gradually lengthens until the increased expansion becomes permanent. Mendel advises an injection of 3 cc. (45 minims) three times daily for a month, to be resumed again as the patient's condition renders it advisable. The local effects are: (1) the cleansing of the larynx; (2) the lessening of the cough and bronchial secretion and the disinfection of the latter; (3) increasing the expansion of the lung so that there is better aëration of the blood. An autogenous vaccine should prove useful, but requires administration over a prolonged period. In an old-standing case at present under treatment by such vaccine the sputum is lessening in quantity and offensiveness and becoming more mucoid.

Surgical treatment has hitherto been too disastrous to render resort to operation advisable except in rare cases. The uncertainty of diagnosis, the infrequency of a single cavity, and the dangers from hemorrhage and other accidents have as yet prevented material advances being made in pulmonary surgery. In cases with a single cavity that can be located, and with obliteration of the pleural cavity at the site for operation, free incision and drainage may give satisfactory results.

A dry climate, free from sudden changes, is most suitable for patients with profuse secretion. For the more robust the bracing, dry air of a northern climate, such as the Canadian Northwest, should be very beneficial; the debilitated will do better in a milder climate, such as that of Southern California, where they can spend many hours with comfort out-of-doors without much exertion or difficulty in keeping warm. In England, Bournemouth, and other places in the south are preferred. Upper Egypt affords probably the most desirable resort in winter, the air of the desert being very dry and not depressing.

BRONCHOSTENOSIS AND BRONCHIAL OBSTRUCTION

Etiology.—Narrowing of a bronchus, even to complete obstruction, may occur in a great variety of acute and chronic affections. The

cause may be situated without or within the tube, or in the bronchial wall itself.

Intrabronchial Causes.—(1) Foreign bodies (discussed under that title), and (2) tumors or diseased glands which grow into or perforate a bronchus.

Extrabronchial Causes.—(1) Pressure from diseased and enlarged bronchial glands. The lymphatic glands lie chiefly at the lower end of the trachea and around the main bronchi, the largest being at the bifurcation. Large quantities of dust particles may mechanically increase the size of the glands to a considerable degree, but the chief causes of their enlargement are the toxins and bacteria of the various diseases in which the bronchi are involved. In the adult, pulmonary tuberculosis is the source of infection of the glands in the great majority of cases. In children the lymphatic glands are normally large and very active, and therefore very liable to become infected, so that the bronchial glands may be greatly diseased, although the lungs are little, if at all, affected.

The bronchial glands may also become infected by malignant or tuberculous diseases of the abdominal organs. The infection may spread to the supraclavicular glands and cause their symmetrical enlargement. This bilateral affection becomes, therefore, a sign of much value in the diagnosis of abdominal and posterior mediastinal diseases. The enlargement of these glands may also occur following tuberculous disease of the cervical glands.

A. Fränkel draws attention to the fact that constriction of the bronchi may be occasionally caused by the pressure of an inflammatory mass resulting from periadenitis. The contraction of the cicatricial tissue produced may also compress the bronchus. In the latter case there may be stridor, contraction of the chest walls, weakened respiration, and dulness. In slowly developing cases the stridor and dyspnoea may be absent.

2. *Aneurysms* of the second part of the arch of the aorta are those most likely to press on the air tubes. They usually develop upward and backward and press at once on the trachea at its bifurcation. As the chest is shortest in all its diameters at the upper part, even small aneurysms may produce marked pressure. The symptoms of bronchostenosis may be the only indications of the condition until severe, even suddenly fatal, hemorrhage occurs. Similar symptoms may arise when the aneurysm is of the innominate or the left carotid artery. Aneurysm of the descending aorta may extend forward and compress the left bronchus.

3. *Mediastinal Tumor.*—The malignant forms are the most important, as by their continued growth they are certain, sooner or later, to press on the bronchial tubes. It is not, however, by pressure on the air tubes alone that they produce their symptoms. Dyspnoea may be caused by secondary deposits in the lungs, pressure upon large vessels, pleuritic effusion, bronchitis, and pneumonia, and by laryngeal spasm excited by pressure on nerves.

The diagnosis may be easy if the signs of a solid mass in the mediastinum are definite, such as dulness beneath and on each side of the

sternum, and in the interscapular region. If the lung tissue over the mass is not completely airless there may be increased vocal fremitus and resonance with tubular breathing; fulness of the veins of the chest or of the neck, with, in many cases, œdema of the corresponding parts owing to pressure caused by obstruction to the return of the blood to the heart; pressure on arteries, as shown by a small pulse; pressure on the laryngeal nerves, causing paralysis or spasm of the laryngeal muscles; and pressure on bronchi, obstructing the entrance of air into the lung.

4. *Abscess* in the mediastinum may be indistinguishable from tumor. It may arise from disease of the bronchial glands, sternum, vertebral column, clavicles, or œsophagus. The following case is a good illustration: A carpenter, aged forty-two, had catarrhal bronchitis, with dyspnoea, beginning in November. The cough was loud and clanging and the sputum frothy. There was the sensation of a valve-like obstruction in the trachea, which was relieved by lying on the left side, but greatly increased by lying on the back. There was rhonchial fremitus, with the increased respiration of exertion, most marked on the right side; coarse, piping rhonchi were audible in inspiration, and a wheeze in expiration. He had intervals of relief until the following February, when the dyspnoea grew much worse, the temperature began to rise, and the sputum became thick, tenacious, and greenish yellow. In a few days the dyspnoea and cyanosis became very marked and rales were abundant. The temperature rose to 102° and pulse to 120. A week later there was a profuse discharge of pus, and he died in a few hours. An autopsy was not permitted.

5. *Syphilitic infection* may involve the bronchial glands. In Hodgkin's disease and leukemia the bronchial glands are frequently affected and often form enormous masses, which may compress the bronchi, especially in children.

6. *Pericardial effusion and dilatation of the left auricle* occasionally become so great as to compress one or both bronchi. Hypertrophy of the heart may possibly compress the left bronchus and the trachea.

Stenosis due to disease of the bronchial wall itself occurs most frequently in the smaller bronchi. Only those affections in which the stenosis causes the chief symptoms should be considered as cases of broncho-stenosis. Among these is a disease first recognized during life by Fränkel, and which he described as *bronchiolitis acuta fibrosa obliterans*. It may be fatal in a fortnight. His attention was drawn to it by Lange's description of the postmortem findings in two cases. The lungs were described as thickly studded with small, white nodules, as in acute miliary tuberculosis, and it was seen that the bronchioles were blocked with new connective tissue. Fränkel's first case was a man who had inhaled caustic vapor in large quantities, and was at once attacked with dyspnoea, which passed off after a time. Repeated attacks of dyspnoea followed. On admission to the hospital there was extreme difficulty in breathing, with cyanosis, and the lungs were greatly increased in volume. No distinct dulness was found, but everywhere small, vesicular sounds were to be heard; there was no fever. There was temporary relief as the acute inflammation following the necrosis of epithelium

caused by the gas abated, but the dyspnoea recurred when the granulation tissue in the injured bronchiolar walls increased and narrowed the bronchioles, in many places even closing them. The autopsy proved the correctness of the diagnosis.

Other causes of stenosis are:

1. Ulcerations following traumatism, as burns, injuries by foreign bodies, etc.

2. (a) Syphilitic ulceration followed by cicatricial contraction; (b) syphilitic peribronchitis; (c) gummata in the walls of the larger bronchi.

3. Tumors of the bronchi.

4. Perichondritis.

5. *Bronchostenosis ecchondritica*, described by Gerhard. In a case there was found marked thickening of many cartilaginous rings and covered by a layer of bone.

6. Spasm is believed to be a cause by some writers.

Pathology.—Besides the constrictions, bronchial dilatations exist above and below the point of constriction, the proximal widening being due to the inspiratory force, and the distal to the expiratory. Emphysema is common. If the obstruction is in a bronchial branch there may be atelectasis of the corresponding portion of the lung.

Symptoms.—The prodromal symptoms of stenosis of the respiratory tract vary with the condition on which it depends. The stenosis, as soon as it causes material obstruction, is characterized by the following symptoms: troublesome, dry cough, occasionally with frothy sputum and streaks of blood; retrosternal pain or distress, usually definitely localized; voice hoarse and broken; constant dyspnoea, more or less severe, with paroxysms of extreme distress, and accompanied by two characteristic phenomena, viz., *coarse, noisy respiration* and *retraction of the chest*.

The *noisy respiration* in marked cases is audible at a considerable distance, and is increased on exertion; it is caused by the air passing through the constricted portion of the tube. It is loudest in inspiration, but occurs also in expiration. On auscultation it is usually loudest over the sternum, but may be most marked in the interscapular region. The loud, sonorous breathing of pharyngeal obstruction is distinguished by its disappearance on pinching the nostrils or closing the mouth.

Retraction of the chest occurs in inspiration and is apparent in the intercostal spaces, the suprasternal notch, the supraclavicular areas, and in the epigastrium. If the stenosis affects only one main bronchus, the retraction is limited to the intercostal spaces of the corresponding side.

A third symptom of importance is the *enfeeblement of the vesicular murmur*, the normal character being at the same time preserved. This phenomenon is observed over the area corresponding to the obstructed tube, so that it may be bilateral, unilateral, or limited to the part of a lung corresponding to a large bronchus.

The urgency of the dyspnoea will depend, first, on the suddenness of the development of the obstruction, and, secondly, on its degree. The sudden closure of a main bronchus causes great, even dangerous dyspnoea.

The marked resulting disturbances of circulation tend to cause œdema in the unobstructed lung and may be quickly fatal. After the shock abates, as well as in cases of slowly forming contraction, even although marked, the dyspnoea may be slight, and material discomfort felt only on active exertion. In children it may resemble asthma and doubtless is often mistaken for it. In long-standing constriction, bronchiectasis in the affected lung is frequently developed. There may be atelectasis or emphysema, and often bronchopneumonia.

Cough is usually present in all well-marked cases of constriction. It may be paroxysmal and of a laryngeal character, or it may resemble whooping cough. In many cases it is short and hacking. The cough varies according as it is excited by the catarrhal inflammation which always occurs at the seat of constriction, the reflex disturbance caused by the pressure of the obstructing agent on the bronchus, or the direct irritation of the recurrent laryngeal or pneumogastric nerve. The last-named cause may affect the voice and also slow the action of the heart.

The sputum is often mucoid, especially in the early stages; later it may become mucopurulent or purulent. Tubercle bacilli may be found in it if a suppurating gland perforates a bronchus. *Hemoptysis* is not infrequent, but is usually scant. It is probably due in most cases to congestion of the mucous membrane at the seat of constriction.

Pain is not uncommon, but rarely marked; it is usually referred to the upper dorsal region, but may also be felt behind the upper part of the sternum. In many patients there is a feeling of pressure deep in the chest. In malignant cases the pain may be severe. Emaciation and fever of a remittent type occur in children when the glands are extensively diseased.

Physical examination will give results varying according to the nature and seat of the obstruction. If a main bronchus is compressed, the expansion of the corresponding side of the chest will be lessened and the normal respiratory sounds feeble or lost, while in the opposite lung the sounds will be exaggerated, the chest increased in size, and the diaphragm lowered. The percussion note will be unaltered on the affected side if no complications in the lung have arisen. If the mass is in the posterior mediastinum there may be dulness in the interscapular region; if in the anterior, there will be dulness over and on either side of the upper end of the sternum. Often in partial occlusion of the bronchus a stridulous inspiratory sound is heard and the vibration may communicate a thrill that can be felt in the chest wall. Eustace Smith states that even in moderate enlargement of the glands at the bifurcation of the trachea a "hum" is audible over the first part of the sternum if the child throws the head well back. He believes the sound is due to pressure on the innominate vein by the enlarged glands which are carried forward by the trachea. The sign is much more rare in the adult. The glands may be so much enlarged as to press upon the œsophagus and cause difficulty in swallowing.

If tuberculous glands soften and form abscesses, they may rupture into the mediastinum and give rise to pyemia and cerebral abscess or into the pleura and cause empyema. A gland may perforate the

trachea or a bronchus and be coughed up and ultimate recovery follow; more usually it causes suffocation, septic pneumonia, or pulmonary tuberculosis. If a gland perforates the aorta a rapidly fatal hemorrhage or embolism will result; if the pulmonary artery is perforated there will be pulmonary infarction or fatal hemoptysis. A double perforation may occur, as into a bronchus and the pleura, causing pneumothorax, or into a bronchus and the mediastinum, causing emphysema.

Diagnosis.—Three principal signs—loud, sonorous breathing, retraction of the chest, and feeble vesicular sounds—are most characteristic. The only affection producing similar symptoms is laryngeal obstruction. In the latter the voice is much more altered and an examination of the larynx shows it to be the seat of the obstruction. Such an examination may demonstrate that the stenosis is tracheal. If the bronchoscope can be used it may show, not only the seat, but also the nature of the obstruction. Furthermore, in laryngeal constriction the larynx makes marked excursions in respiration, while in tracheal and bronchial obstruction it is immobile in breathing as well as in speaking.

The seat of the obstruction, if in the trachea, can be demonstrated by the respiratory sounds being equally affected in both lungs; beside by the mirror and palpation the exact site may be determined. If the obstruction is in either main bronchus or in a large branch, the enfeebling of the respiration will be unilateral in the former case and limited to the lobe in the latter.

Prognosis and Treatment.—These depend wholly on the nature of the cause. In stenosis from syphilis and pressure by aneurism, large doses of potassium iodide may do much good, and even in cases of uncertain diagnosis the iodide may prove of much service. In the paroxysmal dyspnoea caused by the pressure of an aneurysm, inhalation of chloroform, venesection, or hypodermics of morphia and atropine may give relief. In occasional cases of cicatricial stenosis, dilatation of the constriction may be tried by passing graduated sounds through a tracheotomy opening.

Chiari removed, by tracheotomy, a sarcoma from the trachea of a girl, aged eleven years. De Brun resected eleven rings of the trachea in removing a tracheal cancer. The result was satisfactory for five years; death occurred in the sixth year on account of recurrence.

BRONCHIAL CALCULI (BRONCHOLITHS)

The term *bronchopulmonary lithiasis* is applied to the occurrence of stony concretions in the respiratory passages and organs—the *calcareous phthisis* of Bayle. The calculi may be formed in the bronchi, lungs, pleura, or lymphatic glands, and may consist of cartilaginous, bony, or calcareous substance. Bronchial lithiasis is usually a latent condition, calculi being frequently unexpectedly found at autopsy, especially in chronic tuberculosis; but calculi may be formed in other diseases and give rise to symptoms of irritation that simulate tuberculosis.

Clinically, the affection seldom shows signs of its existence except

in the expectoration of calculi; this is of rare occurrence, but was known to ancient writers. Boerhaave described the case of the botanist Vaillant, who expectorated four hundred calculi. In general the number expectorated does not exceed one or two. The "stones" may be cartilaginous, osseous, or calcareous, and the cartilaginous calculi may originate from the tracheal or bronchial cartilages, being set free by ulceration; or from enchondroses of the tracheobronchial cartilages of inflammatory origin (Virchow); or from chondromata of the lung. These calculi have the appearance of cartilage and they can only be differentiated by microscopic examination from cartilaginous masses of fibrous tissue, which may be set free from tuberculous lung by ulcerative processes.

Osseous calculi are distinguished from the calcareous by their microscopic structure showing the presence of osteoblasts and Haversian canals, as in true bony tissue. They may originate from the *bronchial cartilages*, ossification following inflammation of long duration, as in bronchiectasis and pulmonary phthisis; from *pleural ossifications* occurring in old pleurisies; from *pulmonary ossifications* which form in the walls of old abscesses; in tuberculous and non-tuberculous scleroses and in true osteomata, and, very rarely, in the *tracheobronchial mucous membrane*, the seat of old disease.

Calcareous stones are due to the calcification of various tissues of the respiratory organs and to the incrustation of exudates by the deposit of granules of tribasic phosphate of lime and carbonate of lime, without any tendency to ossification. The calcifications in the respiratory organs may be parenchymatous or form in cavities.

In the first group are: calcifications of the tracheobronchial cartilages, as observed in aged persons; calcifications of tuberculous bronchial glands; calcifications in the lung, which may be healthy or previously diseased; calcifications of various tumors; calcifications of the pleura following purulent exudates. In the second class: free concretions in preëxisting cavities and in inflamed dilated bronchi or in pathological cavities of the lung, especially in those of tuberculous origin. These concretions result from the incrustation of stagnant, mucopurulent secretions. They may also be found in the bronchi, around a foreign body of any kind.

FOREIGN BODIES IN THE BRONCHI

Under this heading are included only substances in masses of various sizes, and not particles of solids like dust or fluid substances, as blood or pus, although they too are foreign substances. The accident occurs most frequently in children, but adults also furnish a large contingent. It is a matter for surprise, not that the accident occurs so frequently, but that it is not of much more common occurrence, owing to the fact that anything held in the mouth may, by an accidental reflex inspiration, be drawn into the trachea and thence into the bronchi. The sudden, deep inspiration preceding a laugh or cough, or a strong effort, while the glottis is widely dilated, offers a favorable opportunity for the entrance of the foreign body. During vomiting, some of the ejected

contents of the stomach are liable to be drawn into the trachea by the deep inspiration that immediately follows the act of expulsion. The danger is greatly increased by narcosis.

The danger is greater still during anesthesia, during which the sensitiveness and reflex irritability of the glottis are lessened, as shown by the frequency with which teeth extracted under anesthesia have fallen through the open glottis into the trachea. Pieces of excised tonsil, uvula, polypus, and small instruments used in operating in the mouth, have also fallen or been inhaled into the trachea. In the coma of all intoxications, in all paralytic affections, local or general, involving the larynx, in local diseases of the glottis, as tuberculous and malignant ulceration, and even in natural sleep, the efficacy of the glottic guard is diminished and the liability to the accident therefore increased.

In a group of rare cases the foreign body gains access to the respiratory passage through openings below the glottis, as a tracheotomy wound, a bullet or stab wound, or by ulceration into the trachea of a caseous or calcareous gland. A foreign body in the œsophagus, as a fish-bone, may find its way slowly into the trachea. Pibray, Henry the Fourth's surgeon, recorded the remarkable case of a man coughing up about three inches of his own rib (West).

As a rule the foreign body is carried, as soon as it passes the glottis, to as small a bronchus as can receive it. Not rarely, however, the body lodges for a time in a bronchus of larger size, and is found to descend gradually to a smaller one, requiring some days to reach and become impacted in the smallest tube it can enter. During this time it may be shifted by the cough from place to place in the tube, or moved into other tubes; in these excursions it may be carried up into the trachea and thence drawn into the other lung. Lighter bodies, such as large seeds, may be kept moving back and forth for several days, especially if they strike on the spur at the bifurcation of the trachea or of a bronchus. Foreign bodies are said to pass more frequently into the right than the left bronchus. The position of the patient probably has much to do in determining the course of the foreign body. Thus, if the patient's body is inclined to the left the trachea will be thrown still more into line with the course of the right bronchus, and *vice versa*.

Pathology.—The morbid changes depend on various circumstances, as the length of time the foreign body lodges in the bronchi, whether its surface is smooth or uneven, and, chiefly, whether it is aseptic or carries with it septic organisms. As a rule, if the foreign body be got rid of in a short time, the bronchial irritation excited by its presence soon disappears and no trace is left of the injury; but if it remains long lodged in a bronchus morbid changes result, either at the seat of impaction or in the lung beyond it. The chief danger, however, is not usually from the body itself, whatever its size or form, but from septic inflammation. Particles of pure food may prove harmless in the bronchi and alveoli, being rapidly absorbed, causing at most only a simple catarrh which soon passes away. In the case of larger bodies, however, lodging more than two or three days, chronic inflammation, as a rule, results. The inflammation in addition to the bronchitis may extend to the deeper

parts of the bronchial wall and to the adjacent lung tissue, and lead to more or less extensive fibrosis. This cirrhotic change may extend to the whole of the lung corresponding to the occluded bronchus.

Unfortunately, in the great majority of cases septic changes of greater or less severity occur. If the body be friable it may break up and the parts be carried to other parts of the lung. The septic inflammation in many cases is confined to the bronchial wall, but in a large number septic pneumonia is set up, resulting in local suppuration or gangrene. Frequently only a local abscess is formed which may rupture into a bronchus and the contents, including the foreign body, be coughed up. In such a case the cavity may cicatrize after a time, during which it discharges a gradually diminishing secretion.

In other cases the infection is less virulent and gives rise to a more chronic inflammation, which may produce much interstitial change in the lung. In this manner the whole of the affected portion of lung may become densely fibrosed, with dilatation of its bronchi. *Bronchiectasis* develops in not a few cases, especially when there is only partial occlusion of the bronchus.

When suppuration takes place around an impacted body, it may be found lying loose in the abscess cavity. The abscess may rupture into the pleura, and the body then may lie loose in the empyematous cavity. Such accidents may occur after many years of impaction, during which symptoms were quiescent. In Carpenter's case false teeth were found in the cavity of an empyema at autopsy, thirteen years after they had disappeared down the patient's throat.

Symptoms.—In most cases the entrance of a foreign body through the glottis into the trachea is attended by alarming symptoms of dyspnœa, even of strangulation, owing in part to laryngeal spasm and in part to mechanical obstruction. But in a large minority of cases these symptoms are not extreme; in children they may be so mild as not to attract attention until the body causes dyspnœa by obstructing a large bronchus, or by its movements excites reflex laryngeal spasm. Much will depend on the size, shape, and character of the body, a smooth one causing less disturbance than an angular or pointed one. A large body lodging at the tracheal bifurcation may quickly cause death from suffocation, while a small one, if it passes on in a small bronchus, may produce little, if any, immediate disturbance.

In the beginning of the attack dyspnœa is, as a rule, chiefly due to the laryngeal spasm. This may be excited by even a very small body. The spasm usually passes off soon, unless fresh attacks are induced by movements of the body in the trachea and bronchi, and any persistent dyspnœa that may occur will be caused by the mechanical obstruction to the passage of air. However, the fact should not be overlooked that the foreign body in its passage may injure the larynx and the resulting inflammation after a few hours may cause a gradually increasing dyspnœa which may become extreme. While the dyspnœa is as a rule inspiratory, it is in some cases expressly stated to have been expiratory. This persistent dyspnœa is in some cases marked by exacerbations simulating bronchial asthma; in these the foreign body is evidently movable.

If the body is driven against the glottis during the expiratory efforts of coughing, or even strongly irritates the tracheal bifurcation, the attacks of suffocation may be so severe as to threaten life. The patient gasps for breath, the face becomes livid, the eyes prominent and staring, the veins distended, the heart tumultuous, and a copious perspiration may be poured out. Foam, often mixed with blood, may form in the mouth and nose, and the patient may be thrown into a frenzy of distress or become quite unconscious.

The *physical signs* vary according to the seat and degree of obstruction. If the body is large and lodged in the trachea it will influence the respiration in both lungs, altering the normal breath sounds, lessening expansion of the chest, and producing stridulous inspiratory and possibly expiratory sounds. If the foreign body passes into a bronchus and completely occludes it, there will be complete loss of breath and voice sounds over the lung, or part of it, supplied by the occluded bronchus; but if the occlusion is only partial a stridulous or piping rhonchus that is persistent may be heard; if the occlusion is slight or occurs in a small bronchus, the alteration of the normal signs may be slight or even unrecognizable. If a large bronchus is completely closed, the lung may collapse and contraction of the corresponding part of the thorax follow. But instead of collapse the lung may become consolidated from the occurrence of pneumonia, even within a day after the entrance of the foreign body. In such a case, all communication with the external air being cut off and the bronchi soon filling with exudation, there will be loss of all respiratory sounds.

If only atelectasis occurs, the bronchi being full of air, the signs of consolidation will not be complete. The percussion sound will depend on the amount of air in the bronchi. If the occlusion of the bronchus by the foreign body is partial, the normal respiratory sounds may be only weakened. Sonorous and sibilant rales may be produced as soon as bronchitis occurs around the foreign body, and their existence will be of much diagnostic importance.

If the foreign body be movable it may excite paroxysms of dyspnoea and cough as its position is shifted. If it is small, these movements may lead to its being carried down into a small bronchus, with complete relief of all symptoms until local inflammation is excited. This sudden relief to dyspnoea and cough may lead to the belief that the body has been expelled. In occasional cases there is remarkable tolerance of irritation, and nearly all symptoms may be absent.

The sputum is usually catarrhal at first, but it may be mixed with a small quantity of blood. If the body be angular and sharp, or has remained long in the same place and caused the erosion of a large vessel, bleeding may be profuse and even fatal. The position assumed by the patient may affect the symptoms, especially if the body be movable.

Diagnosis.—If a clear history is obtained and the symptoms are typical, the diagnosis is easy; otherwise, it may present the greatest difficulties. The *x-rays* afford valuable aid, not only proving the presence of the body, but also its exact location. The bronchoscope is the most recent addition to the appliances for examining the interior of the respiratory passages.

In young children the differentiation from laryngismus stridulus may be difficult; and from whooping cough, or even from asthma if spasm occurs, it requires care. If laryngitis is excited, the symptoms of the inflammatory condition may mask those of the foreign body. The most difficult cases are those in which there is no history of the entrance of a foreign body. These cases often present the most anomalous symptoms.

Prognosis.—In the early stage the dangers to life are very great from sudden suffocation or from spasm caused by the body being coughed up against the larynx; in the later stages the danger is from septic changes liable to occur around and beyond the impacted body. In 89 cases of foreign bodies in the air passages reported in the literature, Wood¹ found gangrene in 9 per cent., with deaths in 75 per cent. of these; abscess in 29 per cent., death resulting in all with multiple abscess, and in 30 per cent. of those with single abscess; pneumonia in 11 per cent., and death in 40 per cent.; and bronchitis in 18 per cent., with a mortality of 6.25 per cent.

Although the outlook generally is so bad when the body is not early expelled or removed, there are cases in which it has remained impacted for years and was then spontaneously expelled or removed, perfect recovery following. Burch and Lake² report a case in which a piece of bone was removed from the trachea after being embedded there for nine years; recovery followed. They also give a table of the cases recorded during the last century—31 in all—in which the body had been for a year or more in the lower air passages. In those terminating fatally the cause of death was almost always tuberculosis.

The prognosis varies considerably with the physical character of the foreign body. Hard, smooth ones are less likely to become lodged and are more easily expelled than are the hard, irregular ones. Besides being more likely to become fixed the latter are also more difficult to remove. Fruit seeds are still more unfavorable, especially those that swell in water. Heads of grain are rarely expelled spontaneously, they are difficult to remove even with the aid of the bronchoscope.

Treatment.—To aid in its expulsion, emetics have been given to dislodge the body and permit of its being coughed up. During the straining and vomiting the head is placed below the level of the body so that gravity may favor the falling of the foreign body toward the glottis. Children have been held up by the legs and shaken, or slapped between the shoulders. These proceedings are not without grave risk, as the body by being suddenly impinged against the glottis may cause its spasmodic closure, with danger of suffocation. To obviate this danger tracheotomy is usually advisable, as the conditions for operation are never more favorable than at once after the entrance of the foreign body and before any damage is done to the respiratory mucous membrane. If the body is lying loose in the trachea or one of the larger bronchi, the cough excited by the tracheotomy often causes its prompt expulsion. This was the experience in an unpublished case of a boy,

¹ *Philadelphia Medical Journal*, 1899.

² *Lancet*, 1897, ii, 784.

aged ten, through whose glottis a bean had entered three days before the writer saw him. The bean was moving freely to and fro in the trachea and bronchi, causing paroxysms of dyspnoea from time to time. It was expelled immediately on opening the trachea.

The bronchoscope has proved of great service both in locating and in aiding the removal in cases in which the foreign body has not been expelled by coughing or vomiting. It should be resorted to promptly before the body is carried down into the smaller bronchi. In the case of a boy, aged seven, a revolver bullet was removed by its aid from the tertiary division of the left bronchus, its position having been determined by an x-ray examination. It had entered the right bronchus from which it was dislodged after some days by coughing, entering the left bronchus. Unsuccessful cases should be kept under close observation so as to act promptly if the object becomes dislodged.

Operation has been suggested for the cases in which the foregoing means fail, but the dangers and difficulties of opening the pleura and penetrating the lung are so great that it is seldom advisable. An expectant plan of treatment will probably give the best results.

ASTHMA

Definition.—The pathology of asthma is so imperfectly understood that it is impossible to give a satisfactory definition of the disease. All are agreed that a neurosis is an important factor, but many believe that there is also an inflammatory affection of the bronchioles, either as a primary lesion or at least as an important secondary condition.

Pathologically, the affection is characterized by a spasm of the bronchi and of the respiratory muscles, including the diaphragm, and by vasomotor disturbances of the bronchial mucous membrane. *Clinically*, the disease presents three fundamental symptoms:

1. The *paroxysmal character of the attacks*: These recur at variable intervals; they may even be periodical like those of migraine or epilepsy.
2. The *dyspnoea*: It is characteristic in that it is chiefly expiratory.
3. The *vasosecretory disturbance*: The respiratory mucous membranes throughout become suddenly the seat of an abundant secretion; the mucous membrane of bronchioles, bronchi, trachea, larynx, nasal fossæ, and even the mucous membrane of the nasal duct and conjunctiva participate in this sudden hypersecretion. The secretion of the bronchioles demands chief consideration because of its exceptional viscosity, the nature of the cellular and crystalline elements which it contains, and because of the important part it plays in the mechanism of the paroxysmal dyspnoea.

In addition to these more marked symptoms there are also distension of the chest and depression of the diaphragm.

Etiology.—The essential nature of the malady being unknown, it follows that its fundamental cause must also be in doubt. In view of the fact that it is in the first place a neurosis, the cause must affect the respiratory centre, but the exact nature of the disturbance of this centre we do not know.

Predisposing Causes.—The predisposition to the disease, or more correctly the condition, whether hereditary or acquired, that renders the patient least able to resist the exciting agencies, is the cause of chief importance in essential asthma. Hereditary predisposition is sometimes direct from parent to child, the affection often appearing at the same age in both, and not rarely disappearing at the same age. It may run thus through several generations. It may avoid the direct line and appear in the collateral branches. Sometimes it appears in several members of one family without there being evidence of heredity. Many cases occur in families subject to other hereditary affections, as migraine, epilepsy, and gout. Males are said to be more frequently affected than females, the proportion being about two to one, but the statistics are questionable. The increased frequency of the affection in the male is probably confined to later life, when bronchitis is of more frequent occurrence, and possibly when gout has some influence. The poor are regarded as less often affected than the well-to-do, probably because they are less liable to gouty and lithemic conditions.

Diseases of the respiratory mucous membrane, especially catarrhal conditions of the nasal passages, are of frequent occurrence before the development of asthma. All kinds of cutaneous diseases have been said to render their subjects liable to asthma, however with little, if any, good grounds. To neurasthenia and many other affections influence has been attributed, but with little reason.

Age.—No age is exempt, not even infancy. Probably the majority of cases begin in the early years of life. In 225 cases tabulated by Salter 31 per cent. began before the age of ten years. Few cases of uncomplicated spasmodic asthma begin after fifty, but the affection not rarely develops after that age in persons subject to bronchitis—that is, in early life asthma is generally a neurosis occurring without previous local disease, or independently of it if such exists, while as age advances it is more and more frequently preceded by and dependent upon changes in the respiratory tract. In little children it often disappears after a few attacks and in older children at the time of puberty.

Exciting Causes.—Asthma in the majority of cases is probably due to irritation of the terminals of the nerves in the respiratory mucous membrane by one or more of the many substances suspended in the atmosphere. This view is supported by the effect of many substances, as vapor and emanations from animals, on certain persons, and by the occurrence of asthma in susceptible persons in certain localities only.

Climate and seasons have a very uncertain influence. The malady is probably more frequent from spring to autumn, but this may be due to the greater prevalence of such exciting causes as dust, pollen of grasses and flowers, etc., during this portion of the year. There is also the greatest capriciousness in regard to locality, probably for the same reason. Some patients are better in dry and others in moist places. Many are free in cities and afflicted in the country; or they may even find relief in one part of a city after being affected in another part only a short distance removed.

Affections of the respiratory mucous membrane exist in the great majority of cases, and the paroxysms are probably excited by irritation of the abnormal membrane or some part of it. This is especially true in regard to the nasal mucous membrane in which a certain point may be so sensitive that even touching it may bring on an attack. It is due to this fact that climate and locality have in many cases such influence on the occurrence of the attacks. The nasal mucous membrane when the seat of polypi and thickening from chronic catarrh, and the bronchial mucous membrane when affected by chronic inflammation, are the most important avenues through which the causes that excite the paroxysms act.

Disease of the lungs probably never causes asthma. During acute affections of these organs and of the pleura, in persons subject to asthma, the paroxysms usually disappear for the time being, to return again after recovery. Tuberculous patients rarely suffer from essential asthma, and asthmatic patients seldom become tuberculous, but when they do the asthma usually disappears. Dyspnoea is of frequent occurrence in pulmonary disease, but it is due to a variety of causes other than asthma, as sudden cardiac failure, acute pulmonary oedema, and pulmonary infarct. In affections of the heart true asthma is very rare.

Similarly, in *affections of the kidneys*, paroxysms of dyspnoea are also not uncommon and are due to similar disturbances of the circulation or to uremia, but in these affections true asthma rarely occurs.

Gout as a cause of asthma was first pointed out by Trousseau. He records two cases: in one, a boy, asthma began at the age of five and gout occurred two years later. In the second the asthma was of long standing and gout began at twenty-one years of age.

Functional disturbances of the stomach are apparently the exciting causes in some persons; also those of the intestines, such as flatulence and constipation; relief from these affections may prevent further attacks. Irritation of the ear, of dentition, of the skin, and of the genital tract are also assigned as causes. Paroxysms have also been attributed to intestinal worms. Occasional cases have been met with in which the attacks occurred only during *pregnancy*, and in a few of these cases the disease became permanent toward the end of the child-bearing period.

There are many cases for which we are unable to assign any cause. In some the respiratory centre is so unstable that slight departures from the daily routine may precipitate an attack. Travel may do so, and Fowler mentions the change incident to the rest over Sunday being sufficient to cause such disturbances in digestion and excretion as to be followed by an attack on Monday.

Psychical impressions may be sufficient to excite a paroxysm in neurotic persons. A lady in whom the fragrance of the rose always excited an asthmatic attack was handed one by her physician to test its effect; she took it under protest. A paroxysm immediately followed, although the rose was only an artificial one.

It seems therefore that in very susceptible individuals a peripheral irritation in any part of the body may be sufficient to excite a paroxysm. In the great majority of cases, however, paroxysms are only excited by irritation of some part of the respiratory mucous membrane.

Pathology.—This is a vexed question and cannot be considered in detail in the limits of this article. The general agreement that asthma is at least largely a disease of functional nervous origin indicates that it presents no distinctive morbid changes. Lesions occur in various organs, but no constant change is found and those met with are usually secondary. All chronic cases show various secondary changes of which bronchitis and emphysema are the most frequent.

The essentially neurotic character of asthma is shown by its occurrence in paroxysms, but the greatest uncertainty has existed as to the means by which the paroxysms are excited. Various theories have been advanced to account for them. Of these the most important are:

1. That which attributes the paroxysm to spasm of the circular muscular fibres of the bronchial wall. This theory was first advanced by Williams and is probably the most widely accepted.

2. That which attributes it to swelling of the mucous membrane of the bronchioles from congestion either of vasomotor or inflammatory origin—fluxionary hyperemia (Traube), swelling analogous to urticaria (Clark), vasomotor turgescence (Weber), *bronchiolitis exudativa* (Curschmann).

3. That the paroxysm is due to spasm of the diaphragm or of the inspiratory muscles, or of both.

Other theories, such as paralysis of the bronchial muscles, with consequent loss of expiratory power (Walshe), and spasm of arterioles and œdema of the bronchial mucous membrane, are now scarcely regarded by anyone as possibly correct.

1. In regard to the theory that asthma is due to bronchial spasm, it has been shown that the muscular coat of the small bronchi consists of two interwoven muscular layers, a thick one of circular fibres and a thin, longitudinal one. Under normal conditions the latter is able to prevent narrowing of the lumen of the tube, but if spasm of the circular fibres occurs, the resistance of the longitudinal fibres is overcome by the contraction of the thicker and stronger circular layer and narrowing of the caliber of the bronchus is the consequence. As spasm is never uniform, the narrowing is always irregular.

The effectiveness of bronchial spasm in producing the complete symptom-complex of a typical attack of asthma has been fully demonstrated by the experiments of Brodie and Dixon.¹ They point out that it has been thoroughly established that the vagus is the only motor nerve to the bronchial muscles, and that in the nerve run two sets of fibres, the constrictor and the dilator. Examination of the sympathetic gave negative results so far as the bronchial muscles were concerned.

Stimulation of the constrictor fibres of the vagus could be excited by muscarine, pilocarpine, and electric irritation of the nerve itself or of the respiratory mucous membrane, especially of the upper posterior surface of the nasal fossæ. The stimulation by any of these agencies always resulted in the production of all the signs and symptoms of spasmodic asthma. In all these cases the dyspnoea and distended

thorax are of the typical character, and the sibilant rales are heard on auscultation. There is practically no engorgement of the lungs nor excessive secretion in the bronchi or bronchioles. Furthermore, the attack is at once arrested by subcutaneous injection of atropine, also electric stimulation of the vagus, and that too without disturbing either the heart or the vascular system.

In accounting for the overdistension of the chest they point out that the force of inspiration is much greater than that of expiration, and further, that the *inspiratory act* is violent while the expiratory is quiet and prolonged. The whole endeavor of the patient is to get more air into the lungs, while he is little concerned to drive it out. The exaggerated inspiratory act is required to cause the air to pass through the narrowed bronchioles into the alveoli. The expiratory act, being weaker and acting at growing disadvantage as the chest becomes increasingly distended, and as the depressed fixed diaphragm interferes with action of the abdominal muscles, is unable to empty the alveoli and equalize the ingress and egress of air. Besides, violent expiratory effort would probably further narrow the caliber of the bronchioles by compression, and thus increase the obstruction to the egress of the pent-up alveolar air.

Further evidence in favor of the theory of bronchial spasm is afforded by the sudden onset of an attack in uncomplicated cases and its almost equally sudden cessation. This is the usual course of events in spasm of involuntary muscular fibre, if there are no conditions developed which prevent the complete arrest of the irritation that excites the spasm. In the more chronic cases of asthma, the existence of bronchitis usually alters the typical course of a paroxysm so that the onset becomes less sudden and the termination more gradual and protracted.

2. There is much to be said in favor of the second theory which attributes the paroxysms to congestive swelling of the mucous membrane of the bronchioles and in many cases to exudation into their cavity. Turgescence of the bronchial mucous membrane from vasomotor paresis has been considered by many as analogous to that of the nasal lining, but the structure of the two membranes differs widely. The nasal mucous membrane, especially over the turbinated bones and lower nasal passages, is extremely vascular, and contains large venous plexuses surrounded by muscular fibres forming a kind of erectile tissue (Klein), while that of the bronchi is thin, and its blood supply relatively very scant. Yet the asthma-like dyspnoea occurring in capillary bronchitis proves that swelling of the mucous membrane of the smaller bronchi, either from vasomotor paresis or from inflammation, is sufficient to produce the mechanical condition necessary to induce paroxysms like those of spasmodic asthma. The occurrence of secretion in all but brief paroxysms proves that the membrane becomes at least congested. It is probable that there is only congestion from vasomotor paresis in the less protracted paroxysms, at least in the early period of the affection. The white spirals found in the sputum consist of dense mucus and contain no inflammatory products, showing that they are the product of congestion and not of inflammation. In a fatal case the epithelial lining of the bronchioles was found quite intact and the lumen of the tubes was

filled with mucus (Schmidt). This does not prove, however, that the swelling of the bronchial mucous membrane and the secretion of mucus are the result and not the cause of the spasm of the small bronchi. Sooner or later bronchitis develops in all cases of asthma and probably renders the bronchial mucous membrane more susceptible to irritation. The condition becomes then an important predisposing cause of asthma. Further support is lent to this theory of urticarial swelling of the lining membrane of the bronchioles by the fact that there is great increase in the number of eosinophiles in the blood in both urticaria and asthma.

3. Spasm of the diaphragm and inspiratory muscles as a cause of asthma may be dismissed as quite untenable. The distension of the chest and the spasm of all these muscles are the result, not the cause, of the paroxysm, during which the ingress of air under the greater force of inspiration is in excess of the egress under the lesser force of expiration, so that the chest gradually becomes more and more distended and the diaphragm depressed. The spasm and depression of the diaphragm cause distension of the abdomen and spasm of its recti muscles. This practically paralyzes the abdominal wall, thus destroying the most important agent in forced expiration.

Therefore, the conclusion seems justified that in asthma there is a neurosis which renders it possible for an irritation of a peripheral nerve, generally in some part of the respiratory tract, to be reflected through the vagus to the muscular wall of the small bronchi, causing spasmodic contraction of the tubes and possibly sometimes also, through the vasomotor system, producing hyperemia and swelling of the mucous membrane of the bronchi, generally, if not always, secondary to the bronchial spasm.

Several varieties of asthma have been described according to the region or organ from which the reflex influences exciting the paroxysms emanate, as bronchial, nasal, renal, cardiac, etc. Numerous cases remain in which the origin of the reflex irritation cannot be determined. In this it resembles epilepsy and migraine, in depending upon an abnormal condition of the central nervous system either inherited or acquired. Finally, it may show itself as irritability of the general mucous surface of the respiratory tract, or of certain diseased areas of it, or as a part of general neurasthenia.

Symptoms.—The disease rarely begins suddenly, but in most cases is preceded by a longer or shorter period during which the patient is subject to bronchitic attacks, often with an undue degree of dyspnoea. In time the affection develops, the paroxysms being usually preceded by prodromal symptoms which the patient himself soon recognizes as indicating the approach of an attack. These symptoms vary widely; they may consist of general discomfort, of general buoyancy and vigor, of drowsiness and depression, of epigastric discomfort, of frequent yawning and coryza, with a good deal of secretion and sneezing or itching of the nose, or there may be only a peculiar taste to the saliva, and epigastric oppression without disturbance of digestion or loss of appetite. Whatever the symptoms may be, however, they usually continue of the same nature throughout the history of the case, like an epileptic aura, and always

serve as a warning of a threatened attack; they may make it possible to ward off the paroxysm. Many patients are prone to bronchitic attacks on even slight exposure.

The *paroxysms* may occur at any hour of the day or night, but oftenest about midnight or later. Trousseau said that in his own case the attacks began as the clock struck three in the morning. A late meal often provokes a paroxysm in asthmatics, necessitating their denying themselves this luxury. The patient may go to bed comfortable, and awoken with the attack upon him. It usually begins with a sense of constriction in the throat or around the chest, which threatens to suffocate him. There is a short, dry cough, some wheezing, and distension of the lower zone of the chest. He sits up in bed or rises from it, and sits or stands, desires fresh air, and may open the window to obtain it. He draws it in with all the power of his inspiratory muscles.

When the attack is fully developed he sits with his elbows resting on his knees, his shoulders raised and fixed, his head forward on his hands or at times thrown back on the pillow. Or he may seek a chair, resting his elbows on the arms and his head against the back. Whatever be the favorite position, it is usually maintained until the paroxysm subsides. The object of the position is to raise the shoulders and fix the scapulae, clavicles, and spine, so as to enable the accessory muscles of inspiration to raise the ribs to the farthest possible extent and increase the capacity of the chest to the utmost. The face is pale and anxious at first, but soon becomes livid and swollen, with protrusion of the eyeballs, and as the attack continues the cyanosis becomes very great. There is a copious flow of nasal secretion that provokes sneezing. Profuse, clammy perspiration breaks out and the extremities become cold. All these signs show the great strain to which the right heart is subjected.

The *respirations* become labored and the expiratory part prolonged; they are attended by a wheezing stridor, with sibilant and sonorous rales which may be heard outside the room. The chest is expanded, and on examination the lungs will be found extended downward, the heart and liver being also pushed down. The diaphragm is low and its movements are slight, especially in view of the strenuous inspiratory efforts made by the patient. Notwithstanding the dyspnoea, the respirations may be reduced in frequency, in some cases not exceeding half the normal number. This is owing to the greatly increased length of the expiratory part, which may be two or three or even four times as long as that of inspiration. The pause which normally follows expiration is absent, inspiration following immediately, but there may be a post-inspiratory pause.

The most striking signs to be noted on inspection are the great distension and very limited movement of the chest and the fulness and immobility of the abdomen, although the recti are in a state of strong tension. In inspiration, the soft parts, except the supraclavicular fossae, are but little drawn in, and the epigastrium remains full; all in marked contrast to the recession of these parts observed in obstruction at the larynx or in the large bronchi. *Percussion* gives the hyperresonant note of marked emphysema, the area of cardiac dulness being reduced and hepatic dulness greatly depressed.

On *auscultation* instead of normal vesicular breathing, numerous dry, wheezing, piping rales are heard, most distinctly during expiration, and in some cases in the last part of inspiration. Rhonchus and sibilus develop later, soon followed by moist crepitation. These signs vary from time to time, shifting from place to place, owing to alteration in the spasm of the tubes, the degree of tumefaction of their lining membrane, or to temporary obstruction of bronchi by secretion.

The *voice* is weak and gasping on account of the difficulty of breathing, on which the patient is so intent that he can scarcely utter a word or move.

The attack lasts about two hours, often more, but rarely less. Gradually the intensity of the paroxysm abates and the distress grows less agonizing. Up to this time the patient is unable to cough; now the cough becomes possible and he expectorates small quantities of grayish mucus mixed with froth, in the midst of which are seen small, opalescent, masses—the mucous perles of Laennec. The occurrence of expectoration indicates the termination of the paroxysm. Gradually the respiration becomes fuller and easier. The mucus is extremely tenacious at first, but gradually becomes more abundant and frothy until at length the paroxysm terminates. Usually there is a copious flow of urine with an abundant deposit of urates as the attack ends. The patient now falls into a quiet sleep, to awake refreshed, although somewhat wearied.

Paroxysms may recur regularly at the same hour, continuing for several days or even weeks, at first mild, but growing more severe until they reach the height of severity, after which they gradually abate until they cease altogether. A paroxysm may end, as it began, suddenly, but more often it terminates gradually, especially the paroxysm of longer duration, owing to the greater amount of bronchial secretion caused by the bronchitis that has developed during the attacks.

The recurrences of the attacks of asthma are extremely variable. Few asthmatics escape them, but if the liability is growing less the intervals between the attacks lengthen until they cease altogether. Usually, however, the intervals grow shorter and in many cases the attacks grow in severity, but they may, on the contrary, become less severe. In many persons the attacks, at least in the early stage, occur at certain seasons of the year only, as with the approach of summer, and after a few years in the autumn as well. As the years pass they begin to recur at irregular and more frequent intervals. Fagge refers to a case in which the paroxysms recurred night after night for the last twenty-five or thirty years of the patient's life.

Sometimes the paroxysm continues several days with little abatement, causing much prostration. It scarcely ever terminates fatally. Fagge met with one case in which breathing ceased and restoration was only affected by artificial respiration. In cases with frequently recurring or protracted attacks, chronic affections of the respiratory organs develop, especially emphysema. The breathing is persistently somewhat labored, but typical attacks become increasingly rare, finally ceasing, leaving the patient emphysematous, with exacerbations of dyspnoea simulating the characteristic course of the asthmatic paroxysm. In time the heart

becomes permanently dilated and the condition is the same as that of advanced emphysema.

In some cases the act of inspiration is more labored than expiration, or they may be equally laborious. In other cases there is little if any spasm of the inspiratory muscles, and yet the breathing is labored and accompanied by hissing rales in all parts of the chest, probably due to spasm of the bronchial tubes.

The *sputum* in a true asthmatic attack is quite characteristic. It consists of pellets of grayish-white, semitransparent, tenacious material like boiled tapioca, with a little fine, foamy, thin mucus. The pellets or perles are composed of dense mucus, usually arranged in a twisted manner, the Curschmann spirals, and contain the Charcot-Leyden crystals, degenerated epithelial cells, and leukocytes, of which the majority are eosinophiles. The spirals consist usually of a central solid thread, which may, however, show some vacuoles, and around it the mucus is arranged as a spiral. The spirals vary in the completeness of their formation; some have no central thread or only an indistinct one, or the mucus around them may be arranged in an irregular and imperfect manner, but many show all the parts completely and beautifully arranged. The whole is composed of mucus, the central thread being first formed and therefore the most firm. The twisting has been attributed to a rotatory motion of the cilia of the small bronchi, the motion being made more effective in forming the spirals by the spasm of the bronchial muscles. Hoffmann would explain their formation by the assumption that the whole bronchial tree ends in spirals. If this were the case, minute examination of the lungs should reveal such an arrangement. Curschmann regarded these spirals as occurring in asthma only, and as due to a special kind of catarrh of the finer bronchi. Hoffmann agrees with him and designates it "asthma catarrh." He quotes Schmidt's "investigation of a fatal case which showed that the epithelium of the smaller bronchi was well preserved and that the lumen was filled with a mass of mucus. The winding of this mass could be very nicely followed; it was found to be smallest in the finest bronchioles, and became thicker and thicker as the larger bronchi were approached. In the medium-sized bronchi, where cartilage plates begin to be found, there were seen in a cross-section several such winding figures formed by the union of several smaller bronchi. As typical central threads are found in small bronchi where there are no glands, the threads cannot be regarded as a secretion of the bronchial glands." All are not agreed that these spirals occur in asthma only; some observers report finding them in pneumonia and bronchitis, but the reports require confirmation. If they do occur in these affections it is evidently only in small numbers and not in the large numbers met with in asthma. They are found during the early stage of the asthmatic attack, disappearing when the sputum becomes more abundant and mucopurulent.

The *crystals* are colorless octahedra, small but varying in size, and denser than the other constituents of the sputum. They occur in groups which may be massed into variety of shapes and appear as yellowish or yellowish-green spots. Their chemical constitution is uncertain, but

as they occur in the spiral plugs with degenerated cells they probably result from chemical changes in the latter. By keeping the sputum expectorated during an asthmatic attack in a moist chamber, crystals have occasionally been found to form where there were none previously. They occur almost always in association with the eosinophiles and both disappear together. They have been regarded as identical with spermin crystals, but the latter are larger and are rarely found associated with eosinophilic cells. Similar crystals are met with in leukemic blood, and some observers report having found them in the sputum of bronchitis. Oxalate of lime crystals have also been found; their occurrence is not constant and is probably accidental.

The expired air contains no oxygen or at most only a trace, carbonic acid replacing it.

The catarrhal secretion may be very abundant from the beginning of the attack, constituting the *asthma humidum* of older writers; it may persist after the attack subsides. The patient may have periodical attacks of profuse expectoration without dyspnoea, lasting some hours. Slight *hemoptysis* in the form of streaks of blood is not rare in severe paroxysms. The blood comes from the larger bronchi.

Trousseau first pointed out that asthma may begin as recurrent attacks of coryza with sneezing of extreme violence. The nose runs profusely; the eyes swell and fill with tears; then after a few hours the symptoms subside as rapidly as they set in. During the night a paroxysm of asthma comes on with the usual characters. This series of phenomena may repeat themselves for several days in succession. In some cases the coryza and lacrimation may constitute the whole paroxysm, at least for some time, after which the fully developed attacks of asthma occur.

Of the varieties of symptomatic asthma the most important is *hay asthma* or *hay fever*. It is often associated with typical bronchial asthma or may alternate with it. Many cases beginning as hay asthma gradually change into the ordinary form of asthma, which may in time replace it altogether.

Diagnosis.—In the typical cases of asthma the signs and symptoms are so characteristic that the diagnosis is easily made. The paroxysmal nature of the attack, its sudden onset, the uncertainty of its occurrence, the expiratory dyspnoea with extreme prolongation of the expiration, the expanded and fixed chest, and the depressed, immobile diaphragm are pathognomonic. The presence of large numbers of eosinophiles in the sputum favors the diagnosis of asthma. Spirals and crystals are at least uncommon in other diseases. In *laryngeal and tracheal obstruction* the dyspnoea is inspiratory. The marked respiratory movements of the larynx in the laryngeal affection, the stridor of the inspiration instead of the wheezing of asthma, the contraction of the chest and elevation of the diaphragm instead of the extremely distended chest and the depressed diaphragm of asthma, serve to differentiate these conditions from the latter disease.

The diagnosis of *acute bronchitis* from asthma may present some difficulty, especially in children, in whom asthma is often atypical.

The one often complicates the other, but in bronchitis the dyspnoea is not of sudden onset; it begins and ends gradually, following the onset of the catarrh and not preceding it. Diagnosis is important, as the depressing treatment of asthma may aggravate and prolong the bronchitis.

Asthma and *emphysema* so often coexist that it may be difficult to estimate their relative importance in a given case. During the dyspnoic attack the sputum will serve to differentiate them; in the interval the respiratory capacity of the chest will be much reduced in emphysema and normal in uncomplicated asthma.

Paroxysmal cardiac dyspnoea is distinguished by the quick, panting respiration and the absence of prolongation of the expiratory act.

Enlarged bronchial glands in children may give rise to dyspnoea. In these cases there is usually a short, dry cough, dulness in the inter-scapular region; with irregular fever, wasting, and night-sweats.

Mediastinal tumors and *aneurysm* of the arch of the aorta may, by compressing the trachea or left bronchus, give rise to paroxysmal dyspnoea of an asthmatic type, but it is usually irregular in its symptoms. The brassy cough characteristic of tracheal pressure is usually present, tracheal tugging is sometimes obtained, while dulness over the upper part of the sternum and a heaving impulse may be found.

A *foreign body* in a bronchus can usually be differentiated by the history. In such a case the signs are usually found only in one lung unless the inhalation of the foreign body has been followed by general bronchitis.

A *restless, disturbed sleep* may be due to mild, although unrecognized, asthma. *Hysterical dyspnoea* with spasm of the diaphragm may lead to error if a hasty diagnosis is made. Both inspiratory and expiratory movements are short and there is inspiratory retraction as in laryngeal obstruction. There is no real dyspnoea. The onset of *influenza* may present a remarkable resemblance to asthma. The presence of spirals and crystals with eosinophiles in the sputum of asthma, and of Pfeiffer's bacillus in that of influenza, will determine the diagnosis.

Prognosis.—A paroxysm is rarely fatal. Hilton Fagge's remarkable case, in which artificial respiration was necessary to resuscitate the patient, has been noted.

Age is of more importance in the prognosis than all other considerations, even the severity and frequency of the paroxysms, because elasticity of the lung and integrity of the myocardium are essential to prolonged resistance. The outlook is, therefore, less favorable after middle life. Asthma appearing in childhood may disappear at puberty, especially if the paroxysms are decreasing in severity, if the intervals between the attacks are long and increasing in length, and if the child leads a healthful life in a suitable climate.

In other cases the outlook depends chiefly on the degree of emphysema present and on the condition of the right heart. Not a few chronic asthmatic patients live to old age and die of some other affection. Much depends on the patient's environment. Under the most favorable circumstances many are completely free from paroxysms as well as of all symptoms of bronchial irritation, while in less favorable surroundings they may suffer more or less severely.

Treatment.—Asthma, like other nervous affections, requires variable treatment. Inexplicable idiosyncrasies are as frequent in the action of the remedies as in the action of the causes. One is reminded of the story told of Graves, who is said to have visited two asthmatic patients in the same day; the first attributed his attack to a smoking chimney and the other made his chimney smoke to relieve his attack.

The utter capriciousness of asthma in its response to the action of drugs renders our course of treatment largely empirical, so that in many cases, in the hope of finding one that will succeed at last, one drug after another is tried only to be discarded as useless. While this indicates the method that is generally pursued, the most successful course will be found to be to study each patient carefully in the hope of finding a clue not only to the cause, but also to rational and therefore more probably successful treatment.

The treatment should be directed so far as possible toward the removal of the exciting cause; if successful, complete relief from the affection is usually the result. Search should also be made for the so-called predisposing cause, or for the irritable point on which the exciting cause acts. This is found most frequently in the nasal passages, but may occur in many other parts, as the larynx, trachea, bronchi, stomach, etc. Wherever it is situated it should receive appropriate treatment so as to remove its pathological irritability. The patient's general condition may be at fault and should be restored so far as possible to normal.

In some cases much may be accomplished by systematic respiratory gymnastics in order to develop the capacity of the chest and probably improve the tone of the respiratory centre so as to render its equilibrium less easily disturbed. The judicious and regular use of cold baths to stimulate general vigor may prove of much benefit.

1. **Treatment of the Paroxysm.**—The distress is so great that it usually requires as prompt relief as possible. Patients instinctively turn to those agencies which experience has taught to be most effective.

The *hypodermic injection of morphia* usually gives the most prompt and permanent relief. An initial dose of gr. $\frac{1}{6}$ (0.01 gm.) generally suffices; it may be repeated in about two hours if necessary or a larger dose may be given if due relief is not experienced. A degree of tolerance soon occurs in some cases, but even in these rarely more than gr. $\frac{1}{2}$ (0.035 gm.) will be required. Its use rarely if ever leads to the morphia habit, yet the possibility of such an untoward result should be borne in mind. The existence of bronchitis with much secretion in association with the asthma may render the use of morphia dangerous. In very severe paroxysms strychnine in large doses hypodermically, gr. $\frac{1}{20}$ to $\frac{1}{15}$ (0.0033 to 0.0043 gm.), with some morphia, may give most benefit.

Atropine subcutaneously, judging from the experiments of Brodie and Dixon, should be an effective remedy in allaying the bronchial spasm. It will require to be given in doses sufficiently large to cause full physiological effect. It might be combined with the morphia.

Heroin has of late years been much used instead of morphia and in many cases with gratifying results. It is an efficient respiratory sedative in bronchial affections, relieving cough and causing sleep. It may be

given subcutaneously, gr. $\frac{1}{20}$ to $\frac{1}{6}$ (0.0033 to 0.01 gm.), and repeated in an hour if the paroxysm is not relieved. It requires the same precaution in its use as morphia.

Chloral hydrate has been found by some as efficacious as morphia in suitable cases. It is best given frequently and in small doses, gr. x (0.66 gm.) every hour for the first few doses, after that gr. v (0.33 gm.) until the paroxysm is relieved. It has a depressing effect on the respiratory centres, but unfortunately also on the heart, and therefore it should be given with care in cases with weak heart, if given at all.

Cocaine has been used as a local anesthetic to the nasal passages and throat, but the *cocaine habit* is so easily acquired that its use is too dangerous to be recommended. The local application of an *adrenal* preparation, by causing constriction of the vessels, should prove of much value if the nasal mucous membrane is swollen and turgid.

A perle of *amyl nitrite*, or, probably better, of *amyl valerianate*, broken in a napkin or absorbent cotton and inhaled, or 3 to 5 drops of the fresh solution similarly administered, may bring at least temporary relief. Inhalation of a few drops of *chloroform* sometimes brings prompt and even lasting relief, but there is much danger of its use degenerating into a habit. Inhalations of *ether*, *turpentine*, *ammonia*, and *oxygen* have been used successfully. The efficacy of many liniments applied to the chest is doubtless due to their vapors being inhaled.

Sedative and antispasmodic remedies are largely used, the best being *stramonium*, *belladonna*, *lobelia*, and *tobacco*. Internally the tinctures of the first three require to be given freely, \mathfrak{M} x to xv (0.6 to 1 cc.), and even then they too often fail, especially in the sudden, infrequent attacks.

The fumes from these and many other similar remedies have long been used for the relief of the paroxysm. Various powders, cigarettes, and medicated papers are sold for the purpose. Stramonium, belladonna, and nitrates enter into the composition of most of them. Such efficacy as they possess depends largely on the nitrates and the active principles of the *solanaceæ* in the fumes. Trousseau found a few puffs of a cigar relieved his own attacks. Cigarettes of stramonium and camphor enjoy a reputation. A frequently used powder consists of a combination similar to the following: Stramonium leaves, \mathfrak{J} j (4 gm.); anise, \mathfrak{J} j (4 gm.); tobacco leaves, gr. iij (0.2 gm.); potassium nitrate, \mathfrak{J} j (4 gm.). A teaspoonful to be ignited in an open vessel and the fumes inhaled. The fumes of nitre paper, an old remedy, made by saturating blotting paper with a solution of potassium nitrate (1 to 15), give relief to some patients. See strongly recommended pyridin, 1 dram (4 cc.) being placed in a saucer in the middle of the room. It is a disagreeable, nauseating remedy, liable to cause much depression, and is not therefore to be advised.

None of these inhalations is to be recommended, as at best they rarely bring more than temporary relief, and they may do injury by depressing the heart, whose labors are already fully taxing its powers. The vapor of warm water may prove much better than any kind of smoke. To it may be added such remedies as menthol, benzoin, and eucalyptol.

The use of a hot hand-and-foot bath often brings considerable relief in a short time.

2. **Treatment in the Intervals of the Paroxysms.**—A careful search should be made for the exciting cause so as to remove or avoid it. The condition of the nasal passages demands first attention, as in not a few cases the seat of reflex irritation is found here, and the removal of abnormal conditions may be followed by cessation of the asthma. Too much must not, however, be expected from nasal treatment, and it should be undertaken only for the relief of demonstrable disease. Much injury may be and has been done by the galvanocautery. Many patients experience temporary relief from the treatment and often are reported as cures, so that the literature has become unreliable.

The *diet* should be carefully inquired into; if any articles are found to induce an attack they should be excluded. Constipation should be relieved and the general health made as vigorous as possible, so that the stability of the nerve centres may be raised to the highest degree attainable.

The bronchial mucous membrane should be relieved of all traces of catarrhal inflammation. Cod-liver oil during the winter months may prove useful.

Schäffer is a strong advocate of the *faradic current*, an electrode being placed on each side of the neck about one inch below the angle of the jaw. The current should be fairly strong and used twice daily for fifteen or thirty minutes.

Any *locality* found to induce an attack must be avoided at all hazards. A dry, sandy soil, especially in a dry, pine district is usually most suitable for asthmatics. The district and climate most suitable for the individual must, however, usually be determined by his own experience. Many do well in the dry, bracing atmosphere of the western plains of Canada; others in the milder climates of Florida, Cuba, and California.

Of the drugs which have been used to prevent the recurrences of attacks of asthma, *iodide of potassium* has been of most service. It may be given in doses of gr. v (0.3 gm.) three times a day and gradually increased to three or four times that quantity. It often brings great relief, but it is doubtful if it alone ever effects a cure. Its use should be continued over long periods, two or more years, with a day's omission every eight or ten days. If there is freedom from paroxysms for a long time the dose may be gradually reduced. *Arsenic*, although much less esteemed, is the next most useful drug. In properly selected cases *nux vomica* in ascending doses was considered by Musser quite as valuable a remedy. The cardiovascular remedies are useful when the circulation shows signs of failure.

The mental state demands close attention, as attacks are not rarely precipitated by causes acting on a weak will-power. Psychical treatment becomes of importance in these cases. This can only be carried out satisfactorily in a well-equipped institution where the aid of hydrotherapy, electrotherapy, etc., is available.

CHAPTER XXVII

DISEASES OF THE LUNGS

By HOBART AMORY HARE, M.D.

CIRCULATORY DISTURBANCES OF THE LUNGS

Congestion of the Lungs.—**Etiology and Pathology.**—As commonly employed, two quite different circulatory disturbances of the lung are included under the term congestion, which is therefore subdivided into the active and the passive types.

1. *Active Congestion* (hyperemia of some writers).—In this condition an increased amount of arterial blood is thrown into the lung and consequently it is found in the initial stage of all inflammatory diseases of the lung and pleura, as pneumonia, bronchitis, tuberculosis, and pleurisy. During the cold stage of the paroxysms in malaria and in other diseases accompanied by rigors, an excess of blood is distributed to the lungs. The inhalation of excessively hot or cold air or irritating gases brings about the same state, at times very rapidly fatal. Violent exertion excites active congestion, and athletes have died apparently from this cause alone. Affections of the pons or medulla are possible excitants of the condition, and it may precede the fatal termination of coronary artery disease. A zone of hyperemic tissue surrounds essentially every circumscribed lesion of the lung, whether pneumonia, tuberculosis, abscess, gangrene, or new growth. That active congestion is ever a primary lesion, instead of a symptomatic affection, is extremely doubtful, although many French writers vigorously support this view. In cases of pure active congestion the morbid anatomy and histology are essentially those found in the initial stage of croupous pneumonia.

2. *Passive Congestion.*—This is practically always due to faulty action of the heart, which may depend upon a weak right ventricle or upon obstructive or regurgitant lesions in the left side. To these as causes may be added non-aëration of the lung and compression or thrombosis of the pulmonary veins. Two important types of the condition are observed: (a) brown induration and (b) hypostatic congestion.

(a) *Brown induration*, also called mechanical congestion, accompanies lesions of the left heart which prevent the proper outflow of blood from the lungs. Histologically, the vessels of the lung are distended. The pulmonary connective and elastic tissues increase in amount. In the slowed blood of the distended veins, actual stasis appearing in some areas, increased hemolysis occurs, and pigment from the disintegrated red cells is deposited in the interstitial tissue and in the alveolar epithelium. Chronic bronchitis also ensues. The increased pulmonary

and bronchial tissue causes induration; the pigment gives to the organ a brown color. When incised surfaces are exposed to the air they become bright red from oxidation of the excessive amount of hemoglobin. The sputum contains leukocytes and pigment-bearing cells which have become detached from the alveolar walls. From the nature of the affection primarily responsible for their appearance, the latter are by some writers called "heart-disease" cells.

(b) *Hypostatic congestion* is that form determined by gravity in addition to slowed pulmonary circulation dependent upon weak cardiac action and deficient aëration. It is not uncommon in prolonged febrile diseases, as typhoid fever, and in adynamic states in general. For the latter reason the aged are particularly prone to the affection. Prolonged recumbent posture for any cause favors this form of congestion. It has followed morphia poisoning and is particularly apt to occur in persons suffering from brain lesions, notably those which induce paralysis or coma. The posterior portions of the lungs, or the outer portion of one lung if the patient has lain on that side, are dark in color, heavy, pit on pressure, and on incision drip blood or bloody serum. The vessels in the alveolar walls are distended and the perivascular tissues contain an excess of serum. Under these conditions the serum and less often some blood passes into the vesicles, the air is thereby expelled, and the part sinks when placed in water. To this condition the terms hypostatic pneumonia and splenization have been applied, the latter possibly being appropriate only when considerable blood is in the vesicles. The alveolar epithelium shows granular degeneration and usually more or less extensive desquamation.

Symptoms.—Active congestion of the lungs is characterized by sudden onset, beginning as a rule with a chill and rapidly developing dyspnœa, which is accompanied by sharp pains in the side, cough, and expectoration. The sputum is frothy and contains blood. The temperature may rise to 103° or even higher, but the fever does not persist, falling by crisis on the third or fourth day. Aëration of the lung is diminished, so that cyanosis together with distension of the superficial veins of the neck may be well marked.

The thorax may be somewhat distended, and upon percussion show impairment of resonance. The breath sounds will be found to be harsh and rough, and rales of various kinds may be detected; thus at the base of the lungs fine crepitant or subcrepitant rales may be distinctly audible, while over other parts sibilant and sonorous rales may be detected. Vocal fremitus may also be somewhat impaired. In some cases of active hyperemia the pleura is considerably involved, so that friction fremitus is heard. A slight exudate may also take place. To this form Potain gave the name of pleuropulmonary congestion.

It is evident, therefore, that primary active congestion developing after exposure to cold or injury is, at the beginning of its evolution, not unlike genuine pneumonia.

The symptoms of passive congestion consist in slight shortness of breath upon exertion, and a hard, usually dry cough, which has a tendency to become exacerbated upon the slightest provocation. Expectoration

varies; at times it may be slight or absent, and again it may be of moderate degree. In the latter instance the sputum frequently contains blood. Attacks of hemoptysis may also occur. The vesicular murmur may be diminished and moist rales be plainly heard over the base of the lungs. If the cardiac lesion is aortic instead of mitral, symptoms of pulmonary œdema may manifest themselves.

The symptoms of hypostatic congestion are not definite. As hypostasis develops very slowly in many cases, nothing but slight acceleration of respiration may be present for some time; but when its evolution is more rapid, as for instance in the acute infectious diseases, a pronounced degree of dyspnoea together with cyanosis may appear with comparative suddenness. As soon as exudation occurs and the fluid gravitates, increased fremitus, dulness, and the presence of moist and crepitant rales will be found. The vesicular murmur also is diminished or absent.

Diagnosis.—In regard to active congestion, it is evident from what has been said that the affection possesses no distinctive characteristics. In the beginning it may resemble pulmonary infarction or genuine pneumonia, but as it progresses it will be readily distinguished from both these diseases. From infarction it is differentiated by the disappearance of bloody expectoration and subsidence of other symptoms within a much shorter period than is the case in the former disease. Absence of hepatization and the occurrence of crisis on the fourth or fifth day will serve to distinguish it from croupous pneumonia. The initial chill is said to be less violent than in pneumonia. Primary congestion of the lungs differs from bronchopneumonia both in the manner of onset and evolution, and these differences constitute a means for differential diagnosis. The diagnosis of passive congestion will be made easy by the discovery of the causative cardiac lesion.

Difficulty of breathing and cyanosis developing during the course of an adynamic disease should always arouse suspicion of hypostatic congestion, particularly if no elevation of temperature occurs in association with the other symptoms. From pleural effusion developing in the course of such an affection or in bronchopneumonia, hypostatic congestion can be differentiated by the fact that the level of dulness changes when the patient changes his posture; in effusion too the percussion note is duller than it is in hypostatic congestion.

Prognosis.—In active hyperemia the prognosis is usually favorable, but in some cases œdema may develop with fatal result, or pneumonia be superimposed upon the congestive process, thereby rendering the prognosis less favorable. A few cases following a sudden chill, which resulted from exposure to cold when the patient was in an overheated condition, have been reported as terminating fatally within a few hours. As a rule, however, the symptoms subside within a few days and complete recovery results. Nevertheless, the affection is always to be looked upon as serious, and one demanding active treatment. The prognosis of passive congestion depends largely upon the condition of the heart, which is responsible for it. Owing to the lessened resistance pneumonia may develop and cause a speedy termination of life.

In hypostatic congestion the prognosis varies with the condition in

which it develops, with the vitality of the patient, and the promptness with which the pulmonary involvement is discovered and treated. In the case of old and feeble persons the disease is almost invariably fatal, and in young children the mortality is also very high.

Treatment.—In active congestion prompt measures must be taken to arrest the hyperemic process. For this purpose cups should be applied over the entire pulmonary area. If marked cyanosis is present venesection may be resorted to with good results. If the initial intensity of the symptoms yields, then a stimulating expectorant, such as ammonium chloride, may be employed with advantage, or if preferred the carbonate of ammonium may be used instead of the chloride. Concentrated liquid nourishment must be provided. The dietary mentioned in the article on Bronchopneumonia is appropriate.

In regard to the treatment of passive congestion measures directed to the causative cardiac affection are the ones which will most favorably influence the pulmonary condition. Moderate doses of digitalis together with small doses of strychnine will do good service. Ammonium chloride or benzoate with a small dose of codein or heroin may be useful in allaying the chronic cough. Intercurrent attacks of acute bronchitis are to be treated in the usual manner.

As concerns hypostatic congestion, it may be stated that prophylaxis is quite as important as treatment. Aged or feeble persons who are confined to bed should not be allowed in one position, but should be made to assume a different posture every hour or two. The slightest manifestation of bronchitis in such persons should immediately lead to the institution of treatment. When the disease has once developed the primary indication is to support the heart, and for this purpose digitalis should be given. Hoffman's anodyne is also of value. It may be given every hour in dram doses and digitalis given every four hours, \mathfrak{M} 10 (0.6 cc.) of the tincture being administered until its effect becomes apparent and the frequency of its administration being reduced in accordance with the indications of the individual case. Dry cups should be applied over the base of the lungs posteriorly. Active purgation may do good if the patient's strength is not too low to permit it. In nearly all cases a brisk mercurial purge will do no harm and may do good. If the patient is strong enough, hydragogue cathartics such as magnesium sulphate may be used.

Edema of the Lungs.—**Etiology.**—Localized, collateral, or focal *œdema* occurs in the tissue surrounding circumscribed lesions of the lung, as inflammatory areas, new growths, abscesses, infarcts, and tuberculosis, being congestive and in some instances toxic or inflammatory in origin. General *œdema*, either acute or chronic, is not so readily explained. In the chronic form it accompanies chronic pulmonary congestion, chronic nephritis, cachexia, anemia, cerebral disease, and chronic infections. In cases of slowly oncoming death it may occur as the so-called terminal *œdema*. Regarding this type, Coplin's statistics indicate that too large a percentage of cases has been attributed to this relatively unimportant cause, with the result that an undeservedly lessened significance has become attached to pulmonary *œdema* as a whole. In 2030

autopsies, most of them upon persons dead of chronic diseases, œdema was found in but 405, or 20 per cent., leaving 80 per cent. of deaths unaccompanied by noticeable accumulation of serum in the lungs. Disease of the heart is the most frequently preceding lesion, that organ being affected in 350 of Coplin's 405 cases.

Acute pulmonary œdema occurs particularly in connection with diseases of the kidneys or arteries, although other predisposing causes are alcoholism, extreme cold, and intense mental emotion. Hysteria has been cited as a cause. Of practical interest is the œdema following anesthesia, particularly that induced by ether, and the form developing with various infectious diseases, as typhoid fever, pneumonia, and influenza, this being in favor of the belief that the condition is toxic in origin. This view has been ably upheld by French writers, while most German observers prefer the mechanical theory as an explanation. The classic experiments of Welch led him to believe that pulmonary œdema is due to increased capillary tension, produced by an excess of blood from the right heart over that handled by the partially disabled left ventricle. This is a plausible explanation in some cases, especially the terminal œdemas. Recent studies point to the action of toxins as being an additional if not a paramount factor in many cases. Welch himself now speaks of the frequency with which bacteria, apparently in colonizing numbers, are found in œdematous lungs. The acute pulmonary œdema produced experimentally by the injection of adrenalin very closely simulates that in human beings, but in its development we must admit that mechanical and toxic effects are possibly combined, and hence this cannot be regarded as a type of the condition due purely to circulatory disturbance. On the whole, the most acceptable view as to the etiology of pulmonary œdema is that it is due to increased capillary tension accompanied, aided, and probably in many instances preceded, by degenerative changes, toxic in character, of the capillary endothelium.

Morbid Anatomy.—The base of the lung posteriorly is chiefly affected, but the entire organ may be involved. The œdematous lung is heavy, boggy to the touch, and pale in color, unless darkened by associated congestion, which is frequently present. It pits on pressure and is readily incised. From the incision flows an abundance of frothy serum. At first this is almost clear, but later, especially if pressure upon the lung be made, it becomes blood-stained; the degree of congestion determines the prominence of this feature. The bronchi contain frothy fluid which may be blood-stained. Crepitation is always lessened, but is often present throughout the organ; small patches may be airless. These if excised will sink in water, but they are commonly so small that care in excision is necessary to prevent expressing the fluid. Careful pressure on larger areas will expel the fluid and thus differentiate them from patches of actual consolidation due to inflammatory conditions. Occasionally the affected areas are gelatinoid in consistency, due to partial and probably postmortem coagulation of the œdema fluid; in them, however, fibrin is never abundant.

Microscopically the bloodvessels may be distended, although usually this is not conspicuous and often is entirely absent. The fibrils of the

connective tissue are widely separated by the distended lymph spaces. In the alveoli are few or many leukocytes, variable in type, and a small quantity of residual granular material from the serum. Fibrin may be present, but never in large quantities. Red-blood cells are usually scanty except in cases of acute fulminating œdema, when they are commonly numerous. This accounts for the conspicuous reddish color of the frothy fluid which is often expectorated in extraordinary quantities in these cases. Slight catarrhal bronchitis may be manifest. In the bronchial walls and peribronchial structures, including the lymph nodes, the presence of an excessive amount of serum is evident.

Symptoms.—These consist in rapidly developing dyspnœa, cough, and expectoration. Breathing is very difficult and becomes progressively worse as the exudate continues to accumulate. The patient is anxious and terrified and is fully conscious of the danger which threatens him. As the œdema increases the pulse becomes weak and small, cyanosis changes to lividity, a cold sweat breaks out over the body, the extremities become icy, consciousness is lost, and death ensues under all the manifestations of profound asthenia. The temperature is usually subnormal.

In cases of very rapid evolution, a class to which French clinicians have applied the term hyperacute œdema, a fatal termination may occur within a few minutes after the onset of symptoms. The manifestations of œdema of the lung occurring as the terminal event of exhausting diseases are usually not so violent as those just described, the onset and evolution being more gradual, and the symptoms less pronounced. Expectoration is usually profuse, contains a high percentage of albumin; it is often of a pink or red color.

The physical signs are not characteristic. Upon percussion normal resonance is found to be diminished, particularly over the posterior portion of the lungs. Occasionally small patches of tympany may be found interspersed throughout the dull area. Upon auscultation various rales—fine and coarse, mucous, bubbling, and crepitant—are heard.

Diagnosis.—An adequate history together with the symptoms and physical signs just mentioned will in the majority of cases suffice to make diagnosis clear. Acute œdema might be mistaken for pulmonary embolism, which also has a sudden onset marked by severe dyspnœa. The difference in the character of the sputum and the not uncommon absence of physical signs, or the difference in their character when they are present, will serve to distinguish the latter affection. In uremia the results of the urine examination and the presence of Cheyne-Stokes breathing will afford a means of differential diagnosis. Although the symptoms of hydrothorax are in some respects similar to those of œdema of the lung, the physical signs are different; dulness is more pronounced and its limits vary with the posture the patient assumes. The hyperacute cases, which are fatal in a few minutes, may be confounded with cardiac paralysis or angina pectoris, and postmortem examination be required to disclose the cause of death. If the physician sees the patient while he is still alive the nature of the trouble may be determined.

Prognosis.—This depends upon the underlying causative affection. It is always grave, no matter upon what condition it may depend.

Treatment.—Treatment must be directed both to the immediate source of danger to life—that is, to the œdema, and to the causative affection. For the first purpose, counterirritation in the form of dry cups or a large mustard plaster should always be employed, and in the more urgent acute cases venesection may be used with advantage. When cups are used they should be applied over the entire posterior pulmonary area. Inhalations of oxygen may be tried in the hope that they will allay dyspnoea. The heart must be stimulated by camphor and ether administered hypodermically. A solution containing 1 grain of camphor to 10 minims of ether is well adapted for ordinary use; 10 minims of this solution may be injected beneath the skin every half-hour. Atropine is another drug of value in the treatment of this condition. It is the writer's practice to give gr. $\frac{1}{50}$ (0.0012 gm.) hypodermically for the first dose and then use a smaller quantity at the end of three hours if indications for its employment are still present.

If life is prolonged, strophanthus and strychnine together with hydragogue cathartics, and diuretics, if renal disease be the underlying causative affection, may be used according to the indications of the individual case.

Hemoptysis.—**Etiology.**—The term hemoptysis should be limited strictly to the phenomenon of blood-spitting, but is by common consent interpreted as meaning the ejection of blood in any quantity coming from the respiratory tract. The numerous causes include:

1. Pulmonary tuberculosis, which is by far the most frequent single cause of hemorrhage from the lungs. Usually, the blood comes from eroded vessels which either lie in the walls of cavities, but less advanced disease may cause the symptom. Occasionally, the walls of small vessels infiltrated by the tuberculous process, instead of becoming thrombosed, as they usually do, rupture and give rise to hemorrhage. From this source the quantity of blood is commonly sufficient only to color the sputum, but small quantities of almost pure blood may be expectorated. Stress is placed by some writers upon aneurysmal dilatation of vessels in the tuberculous areas as predisposing to rupture and consequently to hemorrhage. While this change undoubtedly occurs its great frequency is not predicated by autopsy findings.

2. Ulcerative lesions of the larynx, trachea, or bronchi. These usually lead to slight hemorrhage only, but in some cases a vessel of size sufficient to cause serious or fatal loss of blood is eroded. Fibrinous bronchitis may give rise to profuse hemorrhage when the cast is expectorated.

3. Chronic lesions of the heart, especially mitral stenosis, not infrequently give rise to hemoptysis which may occur at intervals for years. The quantity of blood is commonly small.

4. In the initial stage of various inflammatory lesions, as croupous pneumonia, the sputum is often blood-tinged.

5. Abscess or gangrene of the lung.

6. Trauma in the shape of blows upon the chest, or falls, or wounds of the bronchi or lung by foreign bodies aspirated or penetrating from without; under the last is to be included puncture by broken ribs.

7. Leprosy and actinomycosis are among the rarer causes.

8. Malignant growths of the lungs or of the air passages. Ulceration of the tumor may be the direct cause, but intrapulmonary growths may produce it by virtue of the surrounding hyperemia.

9. Emphysema is an unusual cause. When occurring, the amount of blood is commonly small, but the condition has proved fatal.

10. Recurring hemoptysis in subjects of chronic arthritis has been observed.

11. Pulmonary hemorrhage has followed heavy lifting.

12. Bronchiectasis is occasionally complicated by hemorrhage.

13. Diseases accompanied by hemorrhages elsewhere, or by hemorrhagic tendencies, as scurvy, leukemia, and purpura, may cause troublesome bleeding from the lungs.

14. Hemorrhagic infarct of the lung may give rise to hemoptysis.

15. In cases of arrested menstruation, the lung may be the seat of vicarious hemorrhage without showing a definite lesion.

16. During pregnancy and occasionally in some other conditions, hemoptysis without discoverable lesions is encountered.

17. Ware in particular has called attention to pulmonary hemorrhage occurring in young persons who are healthy so far as diagnostic methods are able to determine and who do not afterward suffer from tuberculosis. Of 386 persons exhibiting pulmonary hemorrhage, 62 recovered from that affection and did not later develop tuberculous lesions.

18. Hysteria in some instances appears responsible for pulmonary hemorrhage. The case recorded by Pende is unique. A rugged girl of seventeen developed recurring hemoptysis subsequent to the death of a sister from pulmonary tuberculosis. Stigmata of hysteria were present and signs of pulmonary lesion were absent. The hemoptysis was for a time controlled by suggestion, but finally proved fatal. Autopsy revealed no lesion of the lungs.

19. Aneurysms of pulmonary or neighboring vessels rupturing into the lungs. Among these may be mentioned the aorta, pulmonary artery, the innominate, carotid, and even the subclavian, and the bronchial arteries. From these sources the hemorrhage may be relatively slight if from a small vessel or the partially thrombosed contents of an aneurysmal sac of a large artery, or it may be rapidly fatal if a large sac ruptures.

20. Pulmonary distomatosis (see page 226), known from the cause and the symptoms as parasitic or endemic hemoptysis, is due to the presence in the lung and bronchi of the *Paragonimus westermanii*, one of the flukes.

Symptoms. The circumstances under which hemoptysis occurs, as well as the physical signs associated with it vary with the cause upon which it depends. The bleeding may be very slight or profuse. Thus when it develops as an initial manifestation of phthisis it is often slight, in bronchiectasis it is usually of moderate degree, in advanced phthisis and rupture of an aneurysm it is copious.

As a rule it is sudden in onset, the mouth all at once becoming filled with blood. Persons who have already had attacks, however, may experience prodromal symptoms which warn them of the impending hemorrhage. They have a sense of tightness and constriction in the

chest, some difficulty of breathing and a general sense of lassitude. Soon a sensation of tickling or pricking in the throat ensues, the patient becomes conscious of a salty taste, and the mouth suddenly becomes filled with blood. During an attack the patient is excited and anxious. Unless he is bleeding profusely or unless the hemorrhage has continued for some time, the face is flushed and the pulse rapid. This quickening of the circulation is no doubt partly due to the mental perturbation which is usually present. When a large quantity of blood has been lost symptoms of asthenia are observed; the pulse is then weak, the face blanched, the extremities cold, and syncope may supervene.

Bronchial hemorrhage due either to ordinary severe bronchitis or to cardiac disease does not give rise to symptoms of any consequence unless the alarm which develops may be considered as such.

The physical signs vary with the cause. They have been described under the different maladies with which hemoptysis is associated. Palpation and percussion ought not to be practised during an attack of pulmonary hemorrhage.

Diagnosis.—The most important matter to be determined is whether the blood comes from the lungs, and if so then to ascertain upon what cause the bleeding depends. The principal condition from which hemoptysis is to be differentiated is hematemesis. If the patient be seen during the attack it will be comparatively easy to distinguish between the two by the difference in the character of the blood. Small quantities of blood from the lungs are bright red in color, frothy, and of alkaline reaction. If the hemorrhage be copious the associated symptoms and the history of the case will make the nature of the trouble plain. No reliance is to be placed upon the accounts of the patient or his friends in regard to the character of the attack and the quantity of blood lost. It is not rare to be assured that the patient "bled about a quart," whereas the nurse could prove that only a few ounces were lost.

In regard to the cause of the bleeding, a careful history, together with a subsequent physical examination, will be of the utmost value. Thus if a first attack has been preceded by cough, night-sweats, and loss of flesh the presumption that tuberculosis is the underlying cause will not be improbable. In like manner the discovery of cardiac trouble may explain the origin of certain mild cases. In slight cases of blood-spitting the nose and pharynx should always be examined, as the causative lesion may thus be found. Detection of spurious hemoptysis will depend upon the physician's acumen and knowledge. Blood-spitting occurring in a neurotic or hysterical woman is always suspicious and should put the physician on the alert.

Prognosis.—This depends entirely upon the underlying cause. Although patients are always apprehensive of death during an attack of pulmonary hemorrhage it is very rare for early attacks to terminate fatally. Out of 386 cases observed by the late Dr. Ware, of Boston, only 3 resulted in death during early attacks. Of course, death may take place at once if an aneurysm ruptures or a large vessel becomes eroded. So, too, if blood accumulates in a large cavity respiration may be seriously impeded, pneumonia develop, and death result within a

few days. In advanced tuberculosis long-continued profuse bleeding may so weaken the patient as to cause his death.

In marked contrast to these unfavorable effects of hemoptysis are the results of moderate or slight hemorrhage in cardiac disease. Not only do they do no harm, but they frequently afford relief. The writer is also convinced that temporary relief is often experienced by patients affected with early tuberculosis.

Treatment.—This depends upon the causative factors. In all cases rest is of primary importance. Moreover, if the patient is bleeding and frightened much good will be accomplished if the physician will first of all allay his fears by assuring him that in all probability the attack is not dangerous. Mental excitement and bodily restlessness will thus be overcome. A hypodermic injection of gr. $\frac{1}{4}$ (0.016 gm.) of morphine should be given at once in cases of any severity. It not only quiets the patient, but also allays the cough and thereby prevents fresh attacks of bleeding. If the action of the heart is tumultuous an ice-bag may be applied to the precordium and gr. $\frac{1}{100}$ (0.0006 gm.) of nitroglycerin given every three hours until the blood-pressure is lowered and the circulation subdued. Pieces of ice may also be swallowed.

In hemorrhage due to congestion, counterirritation in the form of dry cups will be found useful. Arterial sedatives, such as chloral, aconite, or veratrum viride, may also be employed with advantage in certain cases. Ergot and astringents, such as lead acetate and gallic acid, are valueless and should not be used. It is doubtful whether chloride of calcium is of any use. Certainly no one would think of giving it to arrest bleeding from a vessel of any size in another part of the body. When due to cardiac disease no treatment other than that directed to the heart is indicated; this form of hemorrhage is usually beneficial.

Embolism, Thrombosis, and Infarction of the Lung.—**Etiology.**—Hemorrhagic infarction or infiltration of the lung (pulmonary apoplexy) is the result of embolism or thrombosis of a branch or branches of the pulmonary artery; the former condition is much more frequently the cause. Emboli may arise from any part of the venous system of the body, thrombosis being the usual primary lesion, the veins of the leg and the uterus and para-uterine tissues being the most common sites. Emboli also originate in the right heart, particularly in the auricle, and in the pulmonary artery. Numerous cases of fat embolism following surgical operations or fractures of bone are on record and fragments of tissue, especially the liver, have been found in pulmonary infarcts. Regarding the frequency of pulmonary apoplexy as compared with the general processes of thrombosis and embolism in the body, it is to be remembered that very small emboli lodging in the lung may give rise to no clinical evidence of infarction, and that massive emboli occluding large arteries cause death so quickly that infarction cannot occur. Thrombosis in the pulmonary arteries depending on pathological changes in their walls is rare. Aufrecht maintains that these changes are due primarily to weakness of the heart resulting from endocarditis, myocarditis, pericarditis, or atheroma of the aorta. Whether or not the sequence of changes is as depicted by him, certain it is that the occurrence

PLATE XVII



Hemorrhagic Infarct of Lung

of pulmonary infarct is favored by enfeebled circulation and that it is most common in chronic heart disease.

Morbid Anatomy.—In the case of embolism of the large arteries, with sudden death, the lung may show no noteworthy changes other than the presence of the occluded vessel. The right lung is most often the seat of infarct unless in one of various possible ways the blood current in the right pulmonary artery is weakened. Infarcts are commonly in the periphery of the lung, the posterior edge at or near the base being a frequent site, but they occur in the interior of the organ. They may be single or multiple and vary in size from 1 to 6 cm. in diameter, although rarely a large part of a lobe is involved. They appear beneath the pleura as approximately circular, elevated, dark-red, or blackish masses that in consistency are quite solid. On section they are more or less perfectly wedge-shaped, the typical infarcted area forming a cone with the base toward the pleura. In some instances, owing to the abundant collateral circulation of the lung, the area is almost globular. At or near the apex of the infarct may often be found the plugged vessel responsible for the lesion. Occasionally careful search fails to reveal such obstruction and in some cases a possible source of emboli is not apparent. These instances are cited in support of the opinion that laceration of bloodvessels may, in the absence of obstructive lesion, cause pulmonary apoplexy, but this view cannot be regarded as established. As a rule, localized pleurisy develops over the affected area and a zone of œdematous lung surrounds the infarct. This zone may be also hyperemic, thus giving to the enclosing band a reddish color as contrasted with the dark hue of the central area. As the infarct ages, the color fades because of disappearance of the blood pigment in the extravasated red cells and small infarcts may return almost to the normal hue. Microscopically the alveolar septa and the vesicles are suffused with blood, the latter accounting for the hemoptysis which so frequently accompanies the process. In cases of fat embolism oil may be detected in the sputa.

The termination of the simple infarct consists in the disintegration and removal of the red-blood cells by phagocytosis or absorption, often with resulting pigmentation of the surrounding pulmonary tissue or neighboring lymph nodes. The embolus may undergo resolution, and if the infarct was small the part may become approximately normal; that the circulation is ever perfectly reëstablished is doubtful. Fibrous tissue formation in the area is nearly always more or less pronounced, in some cases resulting in the substitution of the normal tissue by an irregularly contracted scar. Cases in which the entire infarct separated from the surrounding healthy tissue have been reported. Abscess or gangrene results if pyogenic or putrefactive organisms respectively gain access to the area. If the embolus is composed of tumor cells, a secondary new growth develops in addition to the changes common to non-infected infarcts. Pulmonary emboli arising from suppurative lesions or new-growths are often so small that little or no hemorrhage follows their lodgement in the lung; abscesses or metastatic tumors may therefore develop without the usual phenomena of infarction.

Symptoms.—These vary with the size of the vessels occluded and with the nature of the embolus or thrombus. When the pulmonary artery or one of its large branches is suddenly clogged, the patient is seized with a sense of suffocation and intense dyspnoea and may die within a few minutes. In other cases an attack of syncope comes on; the patient suddenly experiences a feeling of faintness, utters a cry, falls to the ground, and never regains consciousness.

Sometimes when a smaller branch is occluded the onset and termination are not so violent. Symptoms of asphyxia varying in intensity with the size of the vessel which is obstructed are the cardinal manifestations, but the patient does not succumb at once, life being prolonged for several hours. A person affected with this form of embolism or thrombosis presents a striking picture. Respiration is intensely labored, the face is livid, the veins of the neck distended, the nostrils dilated, and the eyeballs protrude from the sockets. The action of the heart is weak and rapid; as the asphyxia advances a cold sweat may break out over the body, it being often the precursor of death. Convulsions have also been known to precede death.

In case small bloodvessels are obstructed infarction results. Very often the first symptom complained of is pain in the side; this is soon followed by difficulty of respiration and within a few hours, by the development of cough and expectoration. The sputum is always blood-stained and is very often entirely sanguinolent, the blood and mucus being intimately mixed. This form of expectoration usually continues for several weeks, but as the infarct undergoes resolution it diminishes in quantity and gradually loses its sanguinolent character. During the course of the affection it is not uncommon for attacks of hemoptysis to occur, but as a rule the quantity of blood lost is not large. In many cases the temperature is not disturbed, but in others slight elevations may take place; they are usually not of long duration. Infective emboli or thrombi may of course produce suppuration or gangrene, in which case hectic fever may be present. Infection of an infarct may also take place through the air passages and likewise give rise to fever. Pneumonia and pleurisy may develop as complications.

Physical Signs.—In the rapidly fatal cases the physical signs are *nil*. In those cases in which life is prolonged a few hours the breath sounds first become weak and then the signs of congestion and œdema develop, so that large bubbling rales and crepitation may be heard. A systolic murmur is also frequently present. In case of infarction dulness will be elicited over the diseased area of the lung. Upon auscultation it is found that the breath sounds are impaired, or perhaps the vesicular murmur may be entirely absent over a circumscribed area. If an area of considerable size be involved bronchial breathing may be heard. Suberepitant and crepitant rales can frequently be detected.

Diagnosis.—The cases in which the pulmonary artery or one of its large branches is suddenly occluded must be recognized by the presence of the symptoms described as belonging to this class of cases. When the patient is known to have suffered with phlebitis or endocarditis no doubt need be entertained in regard to the cause of his sudden illness

and death. Naturally death under similar circumstances may result from angina pectoris, cerebral anemia, or sudden acute pulmonary edema, and the possibility of these affections must be borne in mind. The difference in the type of respiration will serve to differentiate the affection from laryngeal obstruction due to edema of the glottis. The existence of pulmonary infarct will be made plain by the sudden attack of costal pain and dyspnea, the expectoration of bloody sputum, and the physical signs which have just been enumerated.

Prognosis.—Large emboli usually cause death in the manner previously described, although occasionally obstruction of a vessel of considerable size may be followed by subsidence of symptoms within a few hours. In these cases the embolus or thrombus becomes disintegrated and is resorbed. The prognosis of pulmonary infarction cannot be considered unfavorable unless it be due to septic emboli. As a rule, resolution occurs, the symptoms subside, the physical signs disappear, and recovery takes place.

Treatment.—Great care should be taken to prevent the occurrence of embolism and thrombosis. Care should be taken to secure good contraction and involution of the uterus after delivery. In case phlebitis develops, absolute rest together with immobilization of the affected part should be secured and treatment in accordance with the recognized principles of surgery instituted. Those affected with endocarditis should be enjoined to avoid violent exertion of every kind. Absolute rest is of the utmost importance in treating cases which have actually developed, and for this reason when a patient is seen in an attack he should not be disturbed for the purpose of having a thorough examination made.

The principal indication is to support the heart, and for this purpose the diffusible stimulants are most appropriate. Camphor and ether may be given hypodermically, and large doses of aromatic spirit of ammonia may be administered internally. If the patient survive a few hours strychnine and caffeine may then be used. If much restlessness is present a dose of morphia may be given, provided that marked cyanosis is not present to contra-indicate its use. Counterirritation in the form of dry cups may be useful by dilating the peripheral vessels and thus causing an afflux of blood to the surface. If great tension of the right side of the heart is present venesection may afford relief.

For those who survive, rest, nourishing food, and the use of strychnine and caffeine, as already stated, are the appropriate therapeutic measures.

The treatment of infarction is entirely symptomatic. For the pain in the side a mustard plaster or dry cups will often prove beneficial. Sometimes morphia or heroin may have to be used to relieve it. If there is much hemorrhage moderate doses of turpentine, for instance, twenty drops three times a day, may be used with advantage.

BRONCHOPNEUMONIA

Etiology. Under the terms bronchopneumonia, lobular pneumonia, catarrhal pneumonia, and capillary bronchitis is included an affection

so varied in cause and, although to a lesser extent, in pathology as to lead to the suggestion that it be called a lesion rather than a disease. If from these titles, however, bronchopneumonia be chosen, and for many reasons it is the preferable term, the name itself is significant and limits the disease to a quite definite process, even though the causes are exceedingly diverse. Bronchopneumonia, then, is an affection of the lung in which the usual sequence of events is that an inflammation of the smaller bronchioles in scattered areas is succeeded by involvement of anatomically related or of contiguous vesicles. In cases of the primary form the lesion in the two situations possibly begins more nearly simultaneously, but even here the pathology indicates that the exudate first appears in the bronchioles. As to mode of origin the disease is of two types, the primary and the secondary.

Primary bronchopneumonia includes about one-third the cases. In Holt's series of 443 cases, 154 were of this type, agreeing with Conner's conclusion that 30 to 35 per cent. of reported instances are primary. This type comes on without previous general disease, affecting robust, healthy children mainly under two or three years of age. The cause in many instances is the pneumococcus, in this, as in the mode of onset, the affection resembling croupous pneumonia.

Secondary bronchopneumonia is due to many different causes, chief among which are the acute infectious fevers of childhood, particularly measles, whooping cough, diphtheria, and scarlet fever. The age incidence of these diseases determines that this type of bronchopneumonia is chiefly in children below five years of age, although it of course occurs later in life; the latter is especially true of that in typhoid fever, smallpox, and erysipelas, although these diseases are not nearly so frequently complicated by bronchopneumonia as are those of the first group. In addition to these cases of bronchopneumonia occurring in the course of infectious diseases is a second group caused by the entrance into the lung of foreign materials and known as *aspiration* or *deglutition* pneumonia. This occurs in subjects of all ages. In the first, fluids are drawn into the lung. They may be derived from the mouth in cases of infection of that cavity or during operations about the mouth or throat conducted under anesthesia. In other instances the material comes from the lung itself in the shape of fluid from bronchiectatic cavities, blood from pulmonary hemorrhage, or even pus which finds its way into the larger passages. In the deglutition pneumonia solid particles of food gain entrance to the lung. Either fluid or solid material from tumors in the larynx or œsophagus may thus induce bronchopneumonia. Both the aspiration and deglutition forms of the disease are really due to bacteria which pass into the lung with the other material. Some writers prefer not to class these types with bronchopneumonia, but other than the fact that they occur less often than the primary and the other types of the secondary form and finally develop supuration there appears no valid reason for their exclusion.

In addition to these fairly definite causes of bronchopneumonia there are a host of less positive, but nevertheless important, predisposing factors which may play a part in all cases and which in some are of great

significance. Age is an important factor. Young children are particularly the subjects of the disease for the reason that the primary affections causing it by inducing bronchitis are so prevalent among children under five years of age. The primary type of the disease is confined almost entirely to very young children. In a second class of age incidence are old persons, the extremes of life being particularly subject to the disease, although for somewhat different reasons. This type of pneumonia is very often the terminal event in aged and feeble persons who have been suffering from chronic disorders, as nephritis, diabetes, and cardiac affections. It also occurs in these subjects as a complication of acute maladies, but most often follows lengthy and debilitating diseases.

Among the general predisposing factors which may underlie bronchopneumonia is cold, damp, changeable weather. The effect of this is well shown by the greater incidence of the disease in the winter and spring months. Unhygienic surroundings, poor food, insufficient clothing, overcrowded and badly ventilated sleeping quarters, all favor the disease. As a consequence it is more frequent among the poorer classes, is common in the subjects of rickets and other types of malnutrition, and may become almost epidemic in foundling homes and similar institutions. The acute or chronic infections of the respiratory tract, as glanders, leprosy, and anthrax among the less common and tuberculosis as a common form, very frequently induce bronchopneumonia. Possibly in no other disease do lessened powers of resistance of the individual, from whatever cause, play such an important part in determining the inception. This statement is borne out by the wide range of bacteria which under favorable circumstances may serve as exciting agents.

The *bacteriology* of bronchopneumonia, in the present state of our knowledge, forms an unsatisfactory chapter. No specific organism has been isolated. The one most frequently present, alone or associated with other bacteria, is the pneumococcus. In Wollstein's series of 100 cases it was present in 67. It was found in 25 of the 33 cases of primary bronchopneumonia, in 15 of them in pure culture. In the 42 cases of the secondary form in which it was present, it was in pure culture in only 10, thus emphasizing the point already made that it is especially active in the primary form of the disease. Wollstein's studies show also that this organism was present in a greater number of those cases in which a large part of one or more lobes was affected as compared with the instances of widely disseminated and smaller foci. Other organisms found in bronchopneumonia are the streptococcus, particularly in those cases following infectious fevers and in aspiration pneumonia, the *Staphylococcus aureus* and *albus*, and Friedländer's bacillus. In some cases the *Bacillus influenzae* alone is found. In 131 cases of bronchopneumonia found in the 220 fatal cases of diphtheria studied by Councilman, Mallory, and Pearce, the diphtheria bacillus was third in the list of bacteria recovered from the lung, being exceeded only by the pneumococcus and the streptococcus. Single infections are the exception, mixed infections the rule. When the disease is due to the tubercle bacillus it is best considered simply as pulmonary tuberculosis. With this wide range in the bacterial content of the affected lungs, broncho-

pneumonia cannot be grouped with the specific infectious diseases, although the bacterial nature of all cases is not to be doubted.

Morbid Anatomy.—The affected lung may be slightly increased in size or at least does not collapse so readily as usual or even not at all. On the surface, more commonly posteriorly and in the lower lobes, are dark or bluish depressed areas, usually scattered and small, although occasionally they may include a large part of a lobe. These discolored patches show particularly well in the non-pigmented lungs of children. Between these atelectatic areas the lung exhibits a moderate degree of compensatory emphysema. If the condition be well advanced, slightly projecting solid areas may also be detected. These commonly are not large and may be so small that on first examination the organ appears to crepitate throughout; careful palpation, however, reveals the small, airless foci, presenting on the surface and also scattered through the lung as distinct, although often indifferently defined, nodules. These, although not crepitant, lack the pronounced solidity of the consolidated areas in croupous pneumonia. Over the superficial nodules there is often roughening of the pleura or even a fibrinous exudate, this being more marked in the larger foci. The affected part of the lung presents a mottled appearance due to scattered and alternating areas of atelectasis, consolidation, and emphysematous distension. Section of the lung exposes surfaces that are moderately dark red in color, smooth, and bathed with blood or bloody serum or blood-stained mucus. The solidified areas project from the surface to a varying degree, but are never very prominent.

A transverse section of such an area shows the affected bronchus filled with grayish mucus and surrounded by vesicles containing the catarrhal exudate. External to these are the collapsed vesicles of the same or neighboring lobules. Longitudinal section of the pneumonic area shows the racemose arrangement of the bronchus and the infundibula and vesicles filled with the grayish or grayish-yellow, mucoid exudate, some of which can be expressed from the tissue. In some cases these solidified areas are large enough to be excised without obtaining portions containing air, and they then sink in water. In the case of small, widely disseminated foci this test becomes impossible. The intervening collapsed areas are darker in color, smooth, airless, well-defined as separate patches, or, when small in extent, appearing as indistinctly outlined bands passing irregularly between the solidified areas. The bronchi are always more or less inflamed and the peribronchial lymph nodes are usually swollen.

Morbid Histology.—In the affected bronchi is an exudate largely mucoid in character, but containing desquamated and fatty epithelial cells and leukocytes, the former being especially prominent. The bronchial wall is infiltrated with leukocytes and shows evidence of marked oedema. Longitudinal sections may reveal irregular or saccular dilatations of the smaller tubes. The vesicles terminating or surrounding these bronchi are more or less completely filled with a mucoid and cellular exudate similar to that in the bronchi themselves. Fibrin is rarely found and never in quantities approaching that essentially characteristic of croupous pneumonia. The alveolar and bronchial capillaries

are distended, and in the walls of the vesicles are numerous leukocytes, the cellular infiltration of the bronchial and alveolar walls being a conspicuous feature of bronchopneumonia. In many instances the walls of alveoli bordering the solidified areas, and which themselves contain little or no exudate, are occupied by great numbers of leukocytes. In the aspiration and deglutition pneumonias with pus formation, the polynuclear leukocyte predominates and necrotic changes are evident.

The termination in non-fatal cases is usually that of resolution. This process rapidly rids the lung of the non-fibrinous exudate, the blood-vessels and lymphatics caring for that part which is not expectorated. Newly formed epithelium replaces that lost in the desquamative process and the leukocytes and serum in the bronchial and alveolar walls are removed, the affected areas becoming essentially normal. Suppuration frequently terminates the aspiration and deglutition forms of the disease; it is rarely found in the other types. Gangrene occurs in the same kind of cases as does suppuration, occasionally following the latter process. In some instances the affected areas undergo fibrosis.

Symptoms.—As bronchopneumonia arises from the most diverse causes, and as its clinical course depends not only upon the different morbid processes from which it originates and with which it is associated, but also upon the age and previous state of health of the person affected, a comprehensive description applicable to all the forms under which it manifests itself would seem well-nigh impossible. Nevertheless, it is possible to give a general description of its more salient features, afterward discussing its special traits as modified by the causative factors, the extent of the pulmonary involvement, and the age of the patient.

The disease as ordinarily met with in *childhood* usually succeeds bronchitis, which in turn often depends upon one of the acute infectious diseases, so that, as a rule, symptoms referable to the respiratory organs dominate the clinical picture. The bronchial inflammation is generally present for some time before the lungs become involved. The *onset*, therefore, is not abrupt, but insidious. The temperature ascends gradually, respiration becomes difficult, and the cough grows worse. At the expiration of three or four days, pulmonary involvement has become more pronounced and the constitutional symptoms are considerably accentuated. The patient is very restless and is harassed by dyspnoea and cough. The respirations are short, shallow, and very rapid, varying from fifty to seventy-five or even more per minute. The face may be cyanosed and livid, and well expresses the suffering which the patient experiences for want of air. The alae nasi dilate with every breath, and all the auxiliary muscles of respiration are called into play in an effort to force more air into the lungs. This difficulty of respiration may vary in intensity at different times of the day, being worse at night or in the morning, or exacerbations may occur at any time if secretion accumulates or if laryngeal spasm occurs. The cough is more or less severe; it is frequent, hard, and painful, and is accompanied by slight expectoration. In young children there is very little or no expectoration, secretion either being absent or swallowed. The sputum is often blood-stained, but does not have the rusty appearance in croupous pneumonia.

The *fever* varies in severity, and although it may rise as high as 105° it is usually of moderate degree. Preagonal elevations of temperature are not uncommon; they may reach as high as 108° . Morning remissions are marked, although vacillations may take place at any time during the day or night. The temperature falls by lysis, which is protracted over several days.

The *pulse* is very rapid, but its increase in frequency is relatively less than that of the respirations. It is not unusual for it to be as rapid as 140 beats per minute, and it may even become so fast as to be uncountable. The action of the heart becomes weak and irregular and dilatation of the right side may occur.

Anorexia and thirst are always present, and vomiting and diarrhœa are not at all uncommon. The latter may be of toxic origin, or depend upon gastric and intestinal irritation and catarrh resulting from the same exposure to cold that produced the pneumonia. Mucus which has been swallowed may also be vomited.

As regards cutaneous lesions, it is not uncommon to find the characteristic eruptions of the acute infectious diseases with which bronchopneumonia is associated. The heterogeneous rashes of influenza and diphtheria as well as the typical rash of measles are often encountered. The latter, however, is apt to fade rapidly once the pneumonia is developed. In contradistinction to the regularity with which it appears in croupous pneumonia, herpes labialis is rare.

Cyanosis has already been mentioned. When it is pronounced there is very often an associated coldness and clamminess of the skin. Sweating may also occur early in the disease, but it is of a different character than that occurring in conjunction with marked cyanosis, making the skin warm and moist. For the most part the skin is hot and dry during the early stages, but attacks of sweating sometimes occur.

The urine is scanty, high colored, and contains an abundance of salts. Traces of albumin may be found when the fever is high, and larger quantities when such acute infectious diseases as scarlet fever, diphtheria, or influenza have preceded the pulmonary disease.

Pain is not violent, and indeed may be absent. It is not unusual, however, for the patient to complain of dull and occasional shooting pains over the areas of inflammation.

The above clinical picture represents the common form of secondary bronchopneumonia in childhood. Certain variations from this symptom-complex are determined by the extent of the pulmonary lesions, the causative factors of the disease, and the age of the patient. If the foci of consolidation be few in number and scattered throughout the lungs, the symptoms resulting from their presence will not be so severe as those just depicted; the progress of the disease will be slower, its manifestations more irregular, and its duration longer. If, on the other hand, the pulmonary inflammation be massive in extent and constantly advancing, all the symptoms previously described will be intensified. Dyspnœa may become so violent that the patient will suffocate. This condition has been called "suffocative catarrh."

When bronchopneumonia supervenes upon whooping cough or tuber-

culosis, its onset and course are particularly insidious. When it follows whooping cough its progress as a rule is not attended by very acute symptoms. The child is apathetic and sluggish, refuses food, and gradually loses flesh. Some fever is present, but the cough is not pronounced. The physical signs, too, are not well marked. When complicating measles the temperature ordinarily runs a higher and more constant course than it does in many other forms.

In *primary* bronchopneumonia, or that developing irrespective of any antecedent bronchitis, the clinical picture is different from the one we have just drawn. The disease is abrupt in onset, and is often ushered in by chills, high fever, and severe nervous phenomena. The temperature is maintained at a high level, and falls by crisis instead of lysis. The pulmonary symptoms are overbalanced by the constitutional disturbances. The duration, too, is shorter than that of the secondary form. Primary bronchopneumonia is more closely related to croupous pneumonia than is the secondary form.

In the aged and infirm the symptoms resulting from disseminated patches of pulmonary consolidation are frequently masked by the manifestations of hypostatic congestion. The development of the disease is not characterized by any pronounced clinical phenomena. Fever, cough, and dyspnoea may all be absent, and the disease first be discovered when physical examination is made. It often happens, too, that the physical signs are not distinct and that proof of the existence of patches of consolidation is first obtained at autopsy. The chronic bronchial catarrh, with which old persons are so frequently affected, may extend to the bronchioles and produce an exudate with resulting areas of consolidation, and when this is the case the increased severity of symptoms is at first often attributed to a mere exacerbation of the bronchial trouble.

Just as the morbid anatomy and symptoms of bronchopneumonia are variable, so likewise is its duration. It may last from a few days to several weeks. In acute suffocative catarrh and that form superimposed upon the chronic bronchitis of the aged, the disease may terminate fatally within forty-eight hours. The course of the disseminated lobular form is progressive, although irregular, exacerbations occurring as new areas of consolidation develop. Its average duration may be said to be from two to three weeks. When developing in cachectic, strumous children it may last for many weeks. It is unusual for any form of bronchopneumonia to terminate in less than ten days.

Physical Signs.—From what has already been stated it is evident that the physical signs must be variable and inconstant. When only small, isolated, and widely disseminated areas of consolidation exist, percussion will not reveal their presence, and even when considerable consolidation has taken place there may be a sufficient degree of compensatory emphysema to overcome the dulness which otherwise would be elicited. Indeed, a hyperresonant percussion note is very common. It is only when confluence of different consolidated areas takes place, or when the morbid process advances so rapidly as to cause massive consolidation, that marked dulness is detected. It is most common

over the bases posteriorly. When this condition is present, retraction of the sternum and lower ribs is frequently observed.

At first auscultation reveals only the signs of bronchitis. Moist and fine subcrepitant rales will be heard over various areas of the thorax, particularly over the bases posteriorly. If there is consolidation of considerable extent, crepitant rales and bronchophony will replace these sounds. The former may, however, be obliterated if the bronchi become filled with secretion. Over the upper anterior and lateral parts of the thorax, impairment of the vesicular murmur, a prolonged expiratory sound and sibilant rales are not uncommon. Very often these different physical manifestations of the disease exist simultaneously in various parts of the thorax, some being present on one side and others on the other; or they may alternate with one another especially in the protracted forms. They are extremely fugacious and not in proportion with the severity of the subjective symptoms.

Complications and Sequelæ.—Bronchopneumonia may cause complications which materially influence its progress and modify its prognosis. Of the immediate complications, pleurisy, abscess, and gangrene of the lung, and pulmonary hemorrhage must be considered. The pleura is sometimes affected, but the inflammation is usually fibrinous and confined to localized areas, although it may be general. Effusion rarely occurs, but when it does take place it is apt to be purulent. Abscess and gangrene are not common, although the former probably occurs more frequently than the latter. Often abscesses are minute in size, so that they do not cause serious difficulty. If an abscess ruptures into the pleural cavity, an occurrence which is exceedingly rare, but does happen, pyopneumothorax results. Pepper reported a case in which a consolidated area of lung tissue broke down and opened into the pleural cavity, producing pneumothorax.

Both gangrene and abscess are of more frequent occurrence in those forms of the disease dependent upon acute infections, such as measles, diphtheria, and erysipelas, than in those originating from other causes. Gangrene is often associated with noma, which is to be considered as an expression of the same infection which produced the pneumonia; it is not improbable, moreover, that the gangrenous process itself is due primarily to the same cause instead of being secondary to other lesions in the lung.

The expectoration of blood-stained sputum has already been mentioned; it sometimes happens, especially in suffocative catarrh, that enough blood escapes from the intensely congested pulmonary tissues to constitute a slight hemorrhage. Likewise, where there are confluent or extensive areas of consolidation, small vessels may be eroded and permit the escape of blood. These hemorrhages are not of ill omen.

Cardiac involvements such as endocarditis and pericarditis, as well as otitis media and abscess of the brain, are associated conditions depending upon the same cause as the pneumonia. Convulsions and delirium may occur.

The most important sequel and the one most to be dreaded is tuberculosis. It may affect not only the lungs, but the peritoneum

and meninges as well. It must be remembered, however, that bronchopneumonia often develops upon an unsuspected tuberculosis which becomes manifest only as the secondary disease progresses, or is first detected when resolution fails to occur.

Diagnosis.—This may be easy or difficult according to the manner in which the disease manifests itself. Thus it will be readily made when there is a frank expression of the symptoms which we have mentioned as belonging to the usual secondary form as met with in childhood. This is especially true when there is sufficient consolidation to produce bronchial breathing and bronchophony. On the other hand, when the onset and evolution of the disease are particularly insidious, or for instance when it develops during the course of pertussis or tuberculosis, and when it is complicated with chronic nephritis or the cachectic states of the aged, both symptoms and signs may be so ill-defined as to escape notice. Therefore, it behooves the physician to be constantly on the outlook for evidences of pulmonary involvement ensuing in the course of these diseases. Exacerbations during any acute infectious disease or in convalescence therefrom should also direct his attention to the respiratory organs. In this class of cases, however, it is comparatively easy to detect the supervention of bronchopneumonia.

From acute simple bronchitis it is differentiated by the mildness of the symptoms in the former and by the absence of areas of hyperresonance and dullness in different parts of the chest. In bronchitis, moreover, the rales are coarser than in bronchopneumonia. It would be futile to endeavor to distinguish between capillary bronchitis, so-called, and bronchopneumonia, for when the bronchioles are inflamed there is always more or less exudate and consolidation, even though the physical signs pointing to these conditions are obscure or wanting.

From croupous pneumonia, secondary bronchopneumonia is differentiated by the fact that the former attacks persons in good health; that its onset is sudden, severe, and accompanied by a chill; that there is marked prostration in the very beginning of the attack; that the fever is higher and of a continued type, and that it falls by crisis between the fifth and ninth days, most commonly on the seventh; that one lung only is usually affected; that the sputum has a characteristic rusty color; and that herpes labialis is a very constant lesion.

Great difficulty may, however, be experienced in distinguishing between primary bronchopneumonia with diffuse consolidation and genuine croupous pneumonia. The physical signs as related to the consolidated areas are identical in the two diseases, although in bronchopneumonia it is common to find signs of localized areas of disease in other portions of the chest. The character of the sputum in the two maladies constitutes a valuable differential sign, but one which cannot be made use of in children for the reason that secretion is absent or is swallowed instead of being expectorated. It not uncommonly happens that a diagnosis is first made when the temperature falls by crisis between the fifth and ninth day of the illness.

There is a decided similarity between the insidious, subacute forms of bronchopneumonia and tuberculosis. The most valuable means of

distinguishing between the two is by examination of the sputum. In suspected cases in which repeated examinations prove negative an injection of tuberculin may be given, provided, of course, that the temperature has fallen to normal. Small areas of tuberculous consolidation in the apices, together with the associated congestion of contiguous areas, may give rise to subcrepitant rales, and the hectic fever may also resemble the intermittent type of that occurring in bronchopneumonia. Careful inquiry into the family and personal history with a thorough physical examination and search for signs of tuberculosis in other parts of the body, will do much to help the physician in making a correct diagnosis.

Pulmonary congestion occurring in childhood is more sudden in onset and of shorter duration than bronchopneumonia. The temperature is higher and the disease is generally confined to one lung.

Small pleural effusions giving rise to crepitant rales, heard at the upper boundary of the effusion when a deep inspiration is taken, may simulate an insidious bronchopneumonia. Exploratory puncture will clear up any doubt which cannot be overcome by other investigations.

Prognosis.—The same factors which determine the clinical course of bronchopneumonia make its prognosis variable, but the disease is always serious. First the age of the patient must be considered. At the two extremes of life the mortality is particularly high. In children there is a definite relation between age and mortality; the younger the patients the higher the death-rate. Probably from 30 to 50 per cent. of all cases occurring in childhood terminate fatally. In old age, too, the mortality is exceedingly high. The previous health of the patient and also his surroundings contribute not a little in determining the degree of resistance which he can assert in combating the disease. All conditions of faulty nutrition, all weakening influences, such as want of fresh air and sunlight, and proper attention to personal hygiene, as well as such constitutional defects as rickets and scrofulosis, render the prognosis less favorable. Children who are crowded in almshouses, asylums, and charity hospitals do not do so well as they who are more favorably situated. The immediate cause of the disease also exerts a material influence upon prognosis. Thus the disease is especially fatal when it occurs in the course of variola, diphtheria, erysipelas, and measles, as well as when it ensues as a complication of tuberculosis.

Prognosis is also modified by the extent of the pulmonary inflammation. It is evident that the symptoms will be more severe and the chances of recovery less when there is massive involvement of the lungs than when there are only a few widely disseminated areas of consolidation. Among the symptoms which augur ill are marked cyanosis, cardiac failure, Cheyne-Stokes breathing, sudden fall of temperature, hyperpyrexia, delirium, convulsions, and stupor. Pulmonary abscess, unless very minute in size, decidedly increases the danger of death, while pulmonary gangrene is always fatal.

Convalescence is slow and recurrences are common. In primary bronchopneumonia the mortality is not high and recovery is rapid.

Prophylaxis and Treatment.—Much can be done by adequate prophylaxis to reduce the frequency of this disease. As it is of infectious

origin, and as the infection may be either endogenous or exogenous, measures directed both to the proper hygienic care of those not diseased and to isolation of the sick will be of use in lowering its occurrence. As concerns individual prophylaxis, the rules of personal hygiene should be strictly observed. Fresh air, sunlight, nutritious food, proper clothing, regular bathing, and sufficient sleep all increase the resistance.

Since microorganisms potent in the production of this disease are known to inhabit the mouth, special attention should be given to buccal hygiene. Careful and regular cleansing of the teeth, together with the use of antiseptic mouth washes, must be insisted upon. The latter are especially important for those predisposed to diseases of the respiratory organs. Disease of the nasal cavities, pharynx, and tonsils must not be neglected, but receive prompt and skilful treatment. Exposure to dampness and cold must be avoided. Persons predisposed to pulmonary disease should be sedulously excluded from those suffering with pneumonia or bronchopneumonia.

As great a degree of isolation as is compatible with our existing social conditions and present hospital facilities should be practised. An ideal method would be to care for a small number of patients in large, well-ventilated pavilions, thereby doing away with the disadvantages of overcrowding and at the same time securing adequate isolation. Departments in hospitals for contagious diseases might be reserved for patients who develop pneumonia. No doubt its frequency as a complication of the acute infectious fevers, affecting large numbers of children in special hospitals, would be somewhat diminished if this method could be adopted, as it would remove the additional risk of contact infection.

In regard to prophylaxis in the aged and infirm the above rules of hygiene also apply. In addition thereto it is important to prevent this class of persons, whenever possible, from maintaining the dorsal decubitus for long periods of time. Much can be done, too, to prevent the super-vention of bronchopneumonia in convalescence from acute diseases. For this purpose warm clothing and avoidance of exposure to cold are of the utmost importance. The use of antiseptic mouth washes should, of course, never be omitted. The child should never be allowed to lie for any length of time in the same position, especially the dorsal, but should be turned from one side to the other at short intervals. No case of bronchitis in a child should be regarded as a trivial affection.

When bronchopneumonia has actually developed the patient should be placed in a warm, well-ventilated, and well-lighted room, preferably one which is heated by means of an open fireplace. The hot, dry, and not infrequently dust-laden air of rooms supplied with furnace heat is very irritating to the respiratory tract and serves both to make the patient uncomfortable and increase the severity of his disease. It will be found that steam, either natural or medicated, diffused from a bronchitis kettle, will keep the air of the room moist and makes the patient's breathing easier. If medicated steam is desired, a few grains of menthol or a half-dram of tincture of benzoin may be added to the water. Exposure to draughts must be avoided and the temperature of the room must be kept equable.

Our therapeutic efforts must be directed to sustaining the patient's strength, to combating toxemia, and to limiting the extent of the pulmonary lesions.

For the first purpose nutritious, easily digestible food, together with the judicious use of stimulants, is of the highest importance. Milk, koumyss, meat juice, strong broths, and cocoa are suitable articles of diet. Milk holds first rank, but the others may be given alternately with it for the purpose of preventing the patient from becoming tired of an unvaried dietary. All food should be given in small quantity every two or three hours.

Hydrotherapeutic measures, and heat and cold are among our most valuable resources in combating this disease. Cool sponging will reduce temperature, lessen toxemia, and allay restlessness. For the same purpose a full bath of moderate temperature, for instance 85° to 90°, may sometimes be advantageously employed for young children who can be easily lifted from the bed and placed in a bath-tub. Its duration should be from five to ten minutes and it should be accompanied by friction of the surface. Cold affusions will often cause a child suffering with bronchial obstruction to rally and expel the mucus which is oppressing the breathing. The crying and agitation produced by the shock of the cold water have a most beneficial effect. The water used for this purpose should be at a temperature varying from 70° to 60°. An alternate hot and cold plunge may also be employed for this purpose. It should be used only in desperate cases and not repeated too often.

The cold compress to the chest has been strongly recommended. It is made by taking three or four layers of linen, dipping them into water, and then applying them closely around the body from the clavicle above to the umbilicus below. They are then to be covered with a heavy layer of flannel. If the temperature is very high the compress should not be wrung out quite dry, as by leaving more water in it the action will be more protracted and more heat will be abstracted. The compress should be changed every half-hour. An ice-bag to the head will diminish cerebral congestion, lower temperature and relieve pain. Saline infusions are valuable for raising blood-pressure, overcoming toxemia, and stimulating the nervous system; not more than 250 cc. of solution should be given to children. If used for infants 50 cc. is quite enough.

Drugs are to be used first of all to maintain the patient's strength and meet symptoms which arise as the disease progresses. In the beginning of an attack it is advisable to administer a dose of calomel to clear out the intestines. From one-half to one grain may be given in divided doses to infants and young children; to older children and adults two or three grains administered in the same manner is not too much.

The most valuable drugs in the treatment of bronchopneumonia are the stimulants, and of these alcohol holds first place. In those forms originating from the acute infections it is particularly valuable, not only as a stimulant, but likewise combating toxemia to a marked degree. In such cases it should be pushed to its physiological limit. Even young children can consume a considerable quantity in twenty-four hours without manifesting any toxic effects. Infants less than a

year old can take ten to fifteen drops of brandy or whisky in a little water every hour and older children can take from one-half to one dram according to their age. In these cases the drug should be given from the very beginning of the disease. There are few cases, irrespective of their origin, in which alcohol is not indicated.

An old brandy or mature whisky is as a rule the best preparation to use; if the stomach rebels against them champagne may be substituted. Other stimulants of value are Hoffman's anodyne, aromatic spirit of ammonia, and carbonate of ammonia. When the breathing is labored and cyanosis marked, from fifteen drops to a teaspoonful of Hoffman's anodyne, according to the age of the patient, will often afford relief and improve the color. Aromatic spirit of ammonia in like dose may be used for the same purpose. Carbonate of ammonia, gr. j to v (0.06 to 0.3 gm.), every two or three hours, acts both as a stimulant and an expectorant; it must be well diluted and preferably mixed with a little elixir of orange or syrup of acacia.

When the lungs and bronchi are rapidly filling with mucus, a dose of atropine will often arrest the secretion and tide the patient over a critical period. From gr. $\frac{1}{5000}$ to $\frac{1}{1000}$ (0.0001 to 0.0006 gm.) may be given. The atropine may be preceded by an emetic dose of ipecacuanha or apomorphine, which will frequently result in the expulsion of a large quantity of mucus. A moderate dose of strychnine may be combined with the atropine, if desired for its action as a respiratory stimulant. Ether and camphor, given hypodermically, are indicated in severe heart failure. Inhalations of oxygen relieve dyspnoea and lessen cyanosis.

Expectorants are serviceable. Ipecacuanha during the early stages of the disease and ammonium chloride and senega during the later stages are the ones most likely to prove of value.

When racking, painful cough is present, narcotics must be resorted to. They may be given separately or in combination with the other remedies employed. For young children paregoric is probably the safest; for those who are older small doses of codein or heroin may be given with safety, from gr. $\frac{1}{2}$ to $\frac{1}{8}$ (0.03 to 0.008 gm.) of the former and from gr. $\frac{1}{40}$ to $\frac{1}{20}$ (0.0015 to 0.003 gm.) of the latter being administered every three or four hours. During convalescence tonics, such as iodide of iron, arsenic, and cod-liver oil, are indicated. Residence in a warm, dry, southern climate in winter and in the mountains or at the sea-shore in summer will aid complete restoration to health.

CIRRHOsis OF THE LUNGS

Etiology.—Under the names pulmonary cirrhosis, or, the better term, pulmonary sclerosis, interstitial pneumonia, chronic interstitial pneumonia, fibroid lung, and fibroid pneumonia, is included a condition of the lung which in general is quite definite, but which in its manifestations is so variable that satisfactory classification is impossible. This is due to the fact that every inflammatory lesion in that organ may result in the formation of new fibrous tissue and a majority of them

always so terminate. The affection, then, is essentially secondary in character and any etiological division must be based on diverse causative factors. Any classification adopted therefore answers rather to convenience than to scientific accuracy. Certain types of pulmonary sclerosis, however, are predominantly local in origin and development, while others are more diffuse in character.

The localized form of sclerosis is that which develops around or in the lesions of focal diseases of the lung, as gummas, abscesses, infarcts, tumors, and parasitic cysts. Small collections of pigment may result in sclerosed patches in the apices, but commonly this material produces a diffuse fibrosis. The apex also is the common site of local fibroid tuberculosis, a large majority of adults coming to postmortem possessing small foci of this character in one or both lungs. Other chronic infections, as actinomycosis, glanders, and leprosy, may induce localized pulmonary fibrosis.

Diffuse chronic interstitial pneumonia is the result of several pathological processes. Croupous pneumonia occasionally terminates in this manner. For some unexplained reason, possibly the non-production of autolysins, resolution does not occur and the fibrinous exudate collected in the vesicles during the stage of red hepatization is substituted by fibrous tissue. The connective-tissue formation necessarily begins in the alveolar walls, as from this source must be derived the new vessels which appear in the intravesicular new formation. It is held by some that the new tissue is actually formed from the leukocytes in the vesicles rather than from the cells derived from proliferation of connective-tissue elements in the walls themselves. Proliferative changes in the alveolar epithelium may for a time be active during this transformation of the exudate, but eventually the new tissue within the vesicles merges with the thickened, enclosing walls, which take a relatively inactive part in the process, and the area becomes entirely fibroid. Usually this lesion is patchy in distribution, but the parenchyma of an entire lobe may be thus obliterated. To the condition is given the name organizing or organized croupous pneumonia, or gray induration of unresolved pneumonia, or simply the term chronic pneumonia. The last is preferred by some observers who regard the process as practically distinct from the very beginning, in other words, a primary chronic pneumonia rather than an atypical form of the croupous variety. It is by these clinicians said to be more common in debilitated persons; predisposing causes are extreme and long-maintained reduction in temperature and preceding hyperplastic changes in the pleura. Marchand suggests the name chronic fibrous pneumonia.

A second type of diffuse sclerosis is that known as *pleurogenous interstitial pneumonia*. As the name implies, the process follows inflammation of the pleura, generally the plastic type. From the thickened pleura the connective-tissue increase extends into the lung, affecting first the interlobular septa and second the finer fibrous structure of the organ. This process is by some not regarded as a distinct type of fibroid pneumonia, but in origin it differs materially from certain cases in which the lesion in the lung is very similar, that is, the fibrosis which develops in

a lung that has long been compressed by pleural exudate and thereby largely rendered functionless. Here the pleura is also thickened, but there are no adhesions and the pulmonary fibrosis is secondary to the collapse and is general throughout the organ. In the pleurogenous variety the greatly thickened pleura is nearly always firmly adherent to the chest wall and the fibroid areas in the lung can be traced directly inward from the pleura.

Chronic interstitial pneumonia due to the inhalation of dust, whether derived from coal, iron, stone, or other sources, is a relatively common affection elsewhere considered under the heading of *Pneumokoniosis*. The fibrosis is due directly to the chronic irritation of the foreign particles in the tissues, the degree depending upon the amount and character of the inhaled material. Somewhat analogous is the connective-tissue production in chronic congestion of the lung, which is induced by the coexisting venous stasis and the blood pigment deposited in the tissues; this has been discussed as brown induration. Another cause of pulmonary sclerosis is pressure exerted upon the lung by neighboring structures, as new growths and diverticula of the œsophagus, tumors of the mediastinum, and aneurysm of the large thoracic vessels. Pulmonary fibrosis due to syphilis is found in the lungs of the newborn as the so-called white hepatization, due to thickening of the alveolar walls, or in the adult as a diffuse process, beginning usually at the root of the lung and extending outward toward the pleura. At times this syphilitic fibrosis appears to extend from the pleura inward. In either case it represents better than any other of the types mentioned a primary, uncomplicated sclerosis of the lung. Bronchopneumonia may terminate atypically in fibroid changes in some of the involved lobules. In these cases the fibrosis begins as a chronic bronchitis or peribronchitis, invading later the surrounding parenchyma.

Morbid Anatomy.—This varies as does the etiology. In the disseminated forms, which may be bilateral, the affected lung in part or as a whole is more firm than the normal organ and cuts with increased resistance. The fibroid areas, which may be seen through the pleura, present on the cut surface as grayish masses, distinctly circumscribed or radiating from the bronchi as more or less prominent bands marking the interlobar or interlobular septa. These areas are more frequent in the lower lobes and are commonly pigmented. If they are multiple and extensive the intervening lung is emphysematous. The bronchi not infrequently show moderate dilatation. The organ on removal or incision may show little or no tendency to collapse.

The massive type of pulmonary sclerosis differs from the preceding chiefly in degree. It is necessarily unilateral, and while it may affect only a lobe it usually involves an entire lung. The chest wall over the affected organ is less prominent than normal; it may be distinctly sunken, with resulting depression of the shoulder of that side. The heart, which is commonly hypertrophied, and the attached tissues are drawn far to the diseased side, their usual site being occupied by the opposite lung, which is emphysematous, often to an extreme degree. The pleura over the fibroid lung may or may not be conspicuously thickened. In the

cases of pleurogenous pneumonia it is very thick and united to the chest wall by adhesions so dense as to be cut with difficulty when removing the organ. When universal pleural adhesions are absent the lung itself may be extremely small, not larger than a fist, and is drawn inward and backward close to the spinal column. It is firm, cuts with great difficulty, and may be airless. The bronchi are usually dilated, at times to such a marked degree that the bronchiectatic cavities are the most conspicuous features. Evidence of infection is not uncommonly present; this may be pyogenic or tuberculous, more often the latter, and is occasionally manifested by cavity formation. Tuberculosis is often microscopically demonstrable when there is no gross evidence of the disease. In such cases the opposite lung also is usually tuberculous. In the residual parenchyma of the sclerosed lung there is constantly evidence of acute or chronic catarrhal inflammation.

Symptoms.—The changes in the lung may be well advanced before any symptoms other than those of chronic bronchitis, together with slight shortness of breath upon exertion, manifest themselves. The patient may have had a cough of varying intensity for years, being better in summer and worse in winter, but his health has never been seriously impaired. As the sclerosis becomes more extensive, however, and the circulatory area of the lung is progressively diminished the resulting interference with aëration of the blood will give rise to more constant difficulty of breathing than was formerly experienced; the destruction of elastic tissue will likewise contribute to the production of dyspnoea.

As a result of these changes in the lung an abnormal amount of work is thrown upon the right side of the heart, which hypertrophies in an attempt to sustain the burden placed upon it. In course of time compensation may fail, and the symptoms of rupture will then be superimposed upon those produced by the pulmonary lesions. As the heart fails gradually instead of rapidly the access of cardiac symptoms will naturally be slow. The cough and dyspnoea become worse, the patient loses strength and becomes emaciated, may show signs of cyanosis, and in the advanced stages of his malady may become dropsical.

Cough varies with the stage of the disease and the nature of the pulmonary lesions. As already stated it is an early symptom, varies with the season, and becomes progressively worse as the disease advances. If the bronchi are dilated, a condition not at all uncommon, especially when the disease develops as a sequel to bronchopneumonia, the cough assumes a paroxysmal type owing to the effort necessary to force the secretion from the cavities in which it has collected. Under these circumstances it is often worse in the morning than at other times. Retained secretions may undergo decomposition and give rise to fever, which, however, is not of intense degree, the temperature rarely rising higher than 102°. Fever may also be the sign of a tuberculous infection.

In the early stages there is nothing characteristic about the sputum, unless perchance the primary cause is some form of pneumokoniosis, in which case it will be stained by one of the pigments present in this latter affection. When there is bronchiectasis the sputum is especially

profuse and of a mucopurulent character. If the sputum be retained long in a cavity or if the walls of the cavity ulcerate it may become very offensive, and may be blood-stained if minute vessels are eroded. Blood may also be present after failure of the right side of the heart.

Physical Signs.—When cirrhosis of the lung is at all extensive it is accompanied by marked changes in the configuration of the thorax. The contraction and retraction of the lung produce a space in the cavity of the chest, between the surface of the lung and the internal aspect of the thoracic wall, as a result of which the wall retracts. This retraction is particularly marked when there are extensive pleural adhesions. As a rule, the greatest degree of retraction is observed anteriorly between the clavicle and the sixth rib, and posteriorly below the angle of the scapula. The shoulders droop; the intercostal spaces are narrowed; the lateral thoracic wall loses its normal arch, being angular instead of rounded; the apex of the sternum is pulled to one side, and the spine deviates laterally. The respiratory movements are diminished on the affected side. The position of the heart is also altered. When the left lung is affected the apex beat will be displaced upward and outward. Owing to the retraction of the anterior border of the lung the pulsation of the pulmonary artery may be revealed in the second intercostal space. When the right lung is affected the heart will be pulled downward and to the right; displacement may be so marked that the condition may strongly resemble congenital dextrocardia.

Palpation often shows that tactile fremitus is increased. Upon percussion various notes will be elicited. Over the areas of cirrhosis, normal resonance is diminished, or perhaps dulness may be present, especially if the area is large and superficially situated. Areas of compensatory emphysema give a hyperresonance or sonorous sound, while bronchiectatic cavities may emit an amphoric note. When the cirrhotic process affects the right lung the liver ascends and the area of hepatic dulness extends higher than normal, and perhaps may be continuous with pulmonary dulness. On the other hand, when the left lung is contracted, the stomach and intestines ascend, with the result that tympany is heard over the lower portion of the thorax, dulness or impaired resonance being confined to the superior portion of the chest.

The results of auscultation are not distinctive. The vesicular murmur is diminished and bronchial breathing may be detected if there is an extensive area of cirrhotic lung. Over a bronchiectatic cavity amphoric breathing may be heard. Rales and rhonchi of various kinds will be present during the different stages of the disease, as well as when exacerbations occur.

These in general are the physical signs met with in the different forms and various stages of the disease. Their presence depends in part upon the cause of the pulmonary lesion. Thus, dilatation of the bronchi and its accompanying signs are more common when sclerosis develops after bronchopneumonia, deformity of the thorax more pronounced when it occurs as the result of pleurisy with adhesions, and the area of impaired resonance more sharply limited when it follows an unresolved croupous pneumonia. These, however, are only minor differences.

Complications.—Softening of the indurated areas may occur, or tuberculosis be superimposed upon the sclerotic (or softened) areas. Bronchiectasis and cardiac changes have already been considered.

Diagnosis.—In well-developed cases of cirrhosis of the lung in which an accurate history of the development of the disease is obtainable, diagnosis may be made at once with reasonable certainty. In other cases it may be very difficult. The diseases from which it must be distinguished are chronic pleurisy with retraction of the lung, new growths, syphilis, and tuberculosis.

In *pleurisy* with retraction the deformity of the thorax is more irregular than in diffuse cirrhosis of the lung, and the lower portions of the lung are the parts most likely to be affected, whereas in cirrhosis the upper lobes are commonly the site of the disease. Moreover, in pleurisy bronchial breathing is not present, although the breath sounds may be weak or even inaudible. Hemoptysis, although not uncommon in cirrhosis with bronchiectasis, does not occur in pleurisy.

Tumors of the lung and costal pleura often produce contraction and retraction of the lung. Owing to the pressure which they exert and also to the interference which they cause with the ingress of air into the lung, the alveoli collapse, with the result that symptoms and signs similar to many observed in cirrhosis manifest themselves. Under these circumstances differential diagnosis may at first be very difficult, particularly in the absence of an adequate history. In case the growth is malignant, involvement of the neighboring lymph glands, signs of mediastinal compression, and the cachexia peculiar to malignant disease will be the greatest helps in enabling one to form a correct diagnosis. The history of the case, provided that an intelligent and authentic account can be obtained, will also be of great value, particularly information relative to the mode of onset and evolution of the disease. *Syphilis* may produce sclerosis of the lung, giving rise to symptoms exactly the same as those found in other forms of the disease, and unless a syphilitic history can be obtained, signs of syphilis found in other parts of the body, or the Wassermann reaction obtained, no definite knowledge can be had in regard to the origin of the pulmonary disorder.

The discrimination between beginning sclerosis and *incipient tuberculosis* may present many difficulties. Given a patient who has had an attack of croupous pneumonia from which he has never fully recovered, with more or less persistent cough, some difficulty of respiration as time elapsed, perhaps slight elevations of temperature, and presenting, moreover, such physical signs as areas of consolidation, exaggeration of vocal fremitus, and diminution of normal breath sounds, the question which arises is whether he has pulmonary tuberculosis or is beginning to feel the effects of a sclerotic process in the lung. Unless the tubercle bacillus can be found in the sputum, time alone can decide this question. Tuberculosis may be superimposed upon cirrhosis of the lung, and in cases of long standing in which bronchiectatic cavities exist and hectic fever is present, its association may not be suspected unless examination of the sputum reveals the tubercle bacillus. In fibroid phthisis the deformity characteristic of advanced sclerosis is absent, although in

the former disease there is often some flattening of the infraclavicular spaces. The symptoms and signs of the two affections are very similar, and in the earlier stages one may easily be confounded with the other.

Prognosis.—Cirrhosis of the lung is of course incurable, but, as already stated, its progress may be so slow as not to interfere materially with health for many years. This is especially true of the pleurogenous form.

When the disease develops after pneumonia, either lobar or lobular, its course is not so protracted as when it follows pleurisy. Tuberculosis is frequently superimposed upon lobar sclerosis within a short time of the beginning of the malady, and dilatation of the bronchi is often associated with the lobular form. Both these conditions contribute to the severity of the disease and tend to shorten the duration of life. Cardiac complications may cause death in the more advanced cases.

Treatment.—It is evident from what has already been stated that cirrhosis of the lung is an incurable malady. For this reason attempts to prevent it should be made with all the greater assiduity. As the disease is known to develop after incompletely resolved pneumonia, no pains should be spared to secure resolution in every case. For this purpose blisters or other forms of counterirritation to the chest, respiratory gymnastics, residence in a warm, equable climate, with the administration of such drugs as cod-liver oil, arsenic, syrup of hydriodic acid, or iodide of iron are appropriate measures.

Hygienic measures are of the utmost importance. If the patient's means will permit, he should reside in a warm climate where variations of temperature do not prevail, and where there is not much alteration in the degree of humidity. If secretion be profuse, a dry climate, like that of Arizona, for instance, is suitable. High altitudes are of course contra-indicated for persons in the advanced stages of the disease when cardiac complications are present. It is important that the air shall be pure and free from dust. Those who cannot change their residence at will should at least endeavor to obtain as much fresh air and sunshine as they can, and to relinquish occupations entailing the inhalation of dust-laden air. They should remain indoors in inclement weather, and should be warmly clad. It is important to maintain bodily nutrition at the highest possible level, and to secure this end a generous diet should be provided. Highly seasoned, rich, and indigestible food must not be eaten. Tobacco must be interdicted and no alcoholic beverages, other than a glass or two of burgundy or claret at dinner, or a glass of ale with luncheon, should be allowed.

The tonic hydrotherapeutic measures, such as the half-bath of moderate temperature in conjunction with sprinkling of the breast and back with cool water, and later, as the patient becomes more accustomed to the treatment, the use of cool or cold affusions are of decided value in improving nutrition and lessening the liability to contract cold.

As regards treatment by drugs, the early stages of the disease are best managed by the employment of stimulating expectorants for the bronchitis, such as benzoate of ammonium, in 10-grain doses (0.6 gm.) given in capsules after meals, or 5 minims of oil of sandal (0.3 cc.) administered in the same manner. If secretion is profuse, terpin hydrate

may be employed instead. Small doses of codein or heroin may be necessary to alleviate the cough. For acute exacerbations of the bronchitis, ipecacuanha or carbonate of ammonium will be found useful. Inhalations of turpentine or carbolic acid may be employed when bronchiectatic cavities are present. Digitalis must be used according to the usual rules when cardiac compensation begins to fail.

PNEUMOKONIOSIS

Etiology.—Pneumokoniosis is an affection of the lungs developing in those who habitually inspire excessively dust-laden air and is therefore to be classed with the occupation diseases. Chief among the varieties in frequency is *anthracosis* due to the inhalation of coal-dust. *Siderosis* is applied to the condition when particles of iron are inhaled, as in the cases of metal-grinders and nail-makers; in the former more or less stone-dust is almost always associated with the iron. In those who work with stone the affection is known as *lithosis* or *chalicosis*. Kaolinosiis, or clay-workers' disease, has been described and a similar infiltration of the lung occurs in those who handle grain, in those employed in mills dealing with cotton, shoddy, and like materials, and to a lesser degree in street-sweepers and others of similar occupation. From the origin of the condition and its associated lesions, many colloquial names have been derived, as coal-miners' disease, grinders' rot, and miners' or nailers' or stone-cutters' phthisis.

Much of the dust inhaled by all inhabitants of cities does not reach the pulmonary tissues, being returned by the combined action of the secretions and the ciliated cells of the respiratory tract. When the inspired dust is in excess of this protective capacity, as in the occupations named, it passes into and through the alveolar epithelial cells and also those of the finer bronchi and finally reaches the connective tissue beneath. A small part is there retained, the remainder being carried by phagocytes into the lymph stream, by which it is distributed throughout the lung. The researches of Arnold, Hamilton, and others have shown that it is deposited especially in the subpleural interlobular septa, in the peribronchial lymph nodes, and in the perivascular lymph spaces of the alveolar walls. When the process becomes extensive, the sub-sternal and tracheal lymph nodes also become infiltrated.

Morbid Anatomy.—This depends to a large extent upon the quantity and character of the inhaled material, although in general the lesions caused by all are much the same. The most conspicuous is an increase of fibrous tissue, either localized or diffuse in type. As this is the result of irritation by the infiltrated pigment, the degree and extent of the fibrosis vary proportionately with those of the former. The posterior and middle parts of the lung are chiefly affected, especially in moderate degrees of the disease, although some types, particularly anthracosis, may be more prominent in the apices. The anthracotic lung ranges in color from a mottled appearance, due to variously sized patches beneath the pleura and scattered over the cut surfaces, to an organ that

is almost uniformly slaty or even coal-black. From the cut surface of a lung showing the extreme type of the infiltration may in some instances be expressed an ink-colored fluid. In the organs that are not so extremely black, areas variable in size which are gray or grayish black in color, and which are firm and cut with resistance, may be clearly seen on the incised surfaces. These are portions of the lung which have become largely or entirely fibroid, the exact color depending upon the amount of pigment in the sclerosed area. Often these areas are in the form of band-like masses extending inward from the thickened pleura or they may be more marked toward the root of the lung.

The affected organ in some instances is very dark and yet crepitates throughout, but in most cases sections that are quite airless are readily found. These are occasionally so large as to include the greater part of a lobe or of a lung, Osler finding in one specimen a fibroid area 18 by 6 by 4.5 cm. in size. The condition is essentially a chronic interstitial pneumonia, although, as pointed out by some writers, from the general location of the pigment which induces the process it is in origin rather a bilateral chronic productive peribronchitis. The peribronchial lymph nodes are enlarged, firm, and on section show mottled or uniformly dark surfaces. In marked cases the mediastinal lymph nodes also are enlarged, some of them enormously so, and are grayish black in color.

Microscopically, in addition to the increased fibrous tissue, an accompanying catarrhal inflammation can be detected, the epithelium of the alveoli and the smaller bronchioles being granular, pigmented, and desquamating. These pigment-bearing cells are often found in the sputum in large numbers. The denudation of the epithelium reduces the protective powers of the lung against bacteria, and infection is thus rendered more probable, although in at least some instances this exposure appears to be partly or entirely counterbalanced by the presence of the coal-dust, probably aided by the sclerosis. Statistics of a number of observers have been thought to indicate that coal-dust actually militates against the colonization of the tubercle bacillus in the lung, or at least that coal-miners are infected less often than are other individuals. Wainwright, in a study of tuberculosis in the anthracite regions of Pennsylvania, found that the deaths from that disease for ten years at Scranton were 3.37 per cent. for adult mine-workers and 9.97 per cent. for those in all other occupations. Many of the small areas of softening in anthracotic lungs are non-tuberculous and may even be non-bacterial in origin.

Pneumokoniosis due to materials other than coal-dust presents lesions that are in many points similar to those described. In the case of stone-dust the particles tend to form nodules which are gray or dark in color or even give a yellowish tint to the lung, this depending upon the type of the deposited material. These nodules are often exceedingly hard, gritty to the knife, or impossible to section. The surrounding tissue may soften, leaving the concretion in a cavity. If small these pneumoliths may be expectorated.

Associated pulmonary lesions of any of the types of pneumokoniosis include chronic bronchitis, bronchiectasis, and emphysema. The first

named is really a part of the condition itself and often gives rise to the most prominent symptoms of the disease. Enlarged and pigmented bronchial lymph nodes may become adherent to the œsophagus and by softening finally rupture into that structure. The blood stream is in some instances entered by the pigment from peribronchial lymph nodes which adhere to and finally rupture into contiguous veins. In these cases the pigment is deposited in the liver and other viscera and may appear in the urine.

Symptoms.—Pneumokoniosis may persist for years without causing impairment of health, and in cases where it is not of long standing all signs of it may subside in a short time if the exciting cause is removed. As a rule the first symptoms complained of are those of chronic bronchitis. The cough varies in intensity. The sputum is usually scanty, although in some cases it is abundant. It is variously colored according to the nature of the dust which has been inhaled. In anthracosis it is black, in siderosis red, owing to the presence of iron oxide.

As more and more pigment is deposited in the lung, the pulmonary circulation is interfered with, so that signs of emphysema may develop. Reactive inflammation is also often produced by the irritating effects of the foreign substance, the connective tissue proliferating and then contracting, with the result that sclerosis takes place. In either case cough will be intensified, dyspnoea appear, and progressive loss of flesh and strength ensue. Tuberculous infection may take place and cavities form, giving rise to the phenomena of septic infection.

There is nothing distinctive about the physical signs. At first they are those of chronic bronchitis, and later those of emphysema, cirrhosis of the lung, or cavity.

Diagnosis.—This is to be made by the history of the case, the character of the sputum, and the signs of the conditions which develop as the result of the foreign particles in the lung.

Prognosis.—This varies with the extent of the lesions and the possibility of removing the patient from the causative influences. In the stage of chronic bronchitis it is good if the cause can be removed. In the later stages improvement will usually follow removal from exposure to the exciting factors, but when emphysema is once fully established there is, of course, no hope of complete recovery.

It seems probable to the writer that the unhygienic surroundings under which many of the people who are affected with pneumokoniosis live, as well as the excessive use of alcohol to which some of them are addicted, contribute in considerable measure to the supervention of the later stages of their disease, and that if these factors could be eliminated they might pursue their vocations for a longer period without their health undergoing any material degeneration. That the amount of dust inhaled exerts a decided influence upon the rapidity with which the disease becomes serious is well illustrated by Moritz's investigations among the grinders at Solingen, Germany. He found that there were no fork-grinders over forty years of age, while of the total number of knife-grinders 5.5 per cent. were above forty. The fork-grinders work with dry stones, the knife-grinders with moist. Of the scissors-grinders

8.4 per cent. lived to be more than forty. They, too, work with moist stones, the same as the knife-grinders, but they sit farther away from the stones than do the latter and therefore inhale less dust.

Treatment.—Prophylaxis is of greater importance than treatment. The proper ventilation of workshops where the air is laden with dust should be secured, and provision made in mines for the escape of contaminated air through flues. Workmen should be compelled to wear respirators, and should be urged to take as much exercise in the open air as is possible. If all of them could be induced, and did their means permit them, to live in hygienic surroundings the effect no doubt would be most salutary. In this respect, however, the most that the physician can do is to offer advice to individuals in regard to the importance of keeping the windows of sleeping-rooms open, reducing the temperature of the usually overheated living-rooms, the necessity of personal cleanliness, and of the harm from the abuse of alcoholic beverages.

In regard to medical treatment, the indications to be met will depend upon the stage of the disease. For chronic bronchitis the stimulants, such as ammonium chloride, oil of sandalwood, or of eucalyptus, may be employed, either singly or in combination with some preparation of opium. Inhalations of menthol and eucalyptol may also afford some relief. In the latter stages, when emphysema has developed, the measures recommended for that disease are to be employed.

EMPHYSEMA

In the consideration of pulmonary emphysema at least five types, so-called, of the affection are to be noted, namely: (1) Hypertrophic substantive, idiopathic, or large-lunged emphysema; (2) senile or small-lunged emphysema or senile atrophy of the lungs; (3) compensatory or vicarious emphysema; (4) acute vesicular emphysema; (5) interstitial or interlobular emphysema. Although all but the last named of these affect the vesicles, the first only is a distinct pathological and clinical entity for which the term emphysema is entirely appropriate. This type is very clearly differentiated from the others and to it reference is always made when the unqualified term emphysema is employed. For these reasons it seems wise first to consider this form and later briefly to state the chief characters of the other varieties.

1. Substantive or Large-lunged Emphysema.—**Etiology.**—Very many factors have been assigned as the chief or contributing cause of this disease. Two points appear definitely established, namely, that emphysema occurs rarely or never in lungs that are not congenitally weak, and, second, that the actual exciting cause is increased intra-vesicular tension. So far as the first factor is concerned the disease is hereditary in that the predisposition is transmitted in the shape of pulmonary tissue that is unable successfully to withstand heightened intra-alveolar pressure. This view receives strong support from the number of family series of cases reported and also from the not infrequent development of the disease in childhood. The condition in the parents most often underlying this tendency is emphysema itself, but gout

appears worthy of mention. The fundamental nature of the inherited weakness has not been clearly determined. A defect in the elastica of the lung is the most reasonable supposition, and although this has not been proved and possibly is incapable of satisfactory demonstration, it nevertheless best explains the changes that occur. Heightened intravesicular pressure may be brought about by forced inspiratory or expiratory action. This factor is undoubtedly active in the production of compensatory emphysema, but that it is of considerable importance in the type under consideration is to be regarded as doubtful. When lobules or parts of lobules are eliminated from the air-containing capacity of the lung by varied processes, particularly in the nature of inflammation of the smaller bronchioles, the neighboring vesicles become at least temporarily overdistended. This is admitted by all, and if the plugged areas remain permanent, typical compensatory emphysema results. To induce a universal distribution of the lesion, the obstruction must shift, and thus in succession bring all parts of the lung under the increased strain. If this repeatedly occurs the elasticity of the vesicular walls finally becomes permanently lessened and an overdistended condition of the vesicles is the result. From the very nature of this process it does not appear that it can be held accountable for the production of the great majority of the cases of large-lunged emphysema.

The *expiratory factor* in the production of increased intravesicular tension and consequently of emphysema must now be regarded as a more satisfactory explanation. It is brought about by increased pressure upon the lung by the chest wall at the time when free egress of air from the organ is prevented by abnormal conditions in the respiratory passages, particularly the narrowing of the glottis that occurs during coughing. By inducing the violent expulsive efforts made during this act, chronic bronchitis is one of the most fruitful causes of emphysema. Whooping cough is also a cause. During these efforts the sternum and costal cartilages are pushed forward, the ribs become less oblique, the outer and posterior parts of the lungs are subjected to increased pressure, and the spaces in which lie the apices and anterior margins of the organs are made more capacious, thus permitting overdistension of the vesicles in those areas. Confirmative of this explanation is the fact that in these locations emphysema first appears and later becomes most conspicuous. The increased tension produced in the lungs of glass-blowers and the players of wind instruments, as well as that induced by heavy lifting also tends to produce emphysema. That they are so important as at one time believed, however, is not borne out by recent clinical and anatomical studies, it being shown that with care a wind instrument can be blown without injuring the lungs of the player. It may be said in conclusion that doubtless in some cases both inspiratory and expiratory distension are active in the production of emphysema, the former especially in those parts of the lung subjected to greatest pressure by the thoracic wall. In chronic bronchitis there is not infrequently the foundation for both series of phenomena.

In the etiology must be included those conditions which tend to produce bronchial or other changes that in turn cause increased expiratory

effort. Among these should be mentioned the inhalation of the various types of dust. Of actual predisposing diseases, bronchitis and asthma are the most important. Regarding age, substantive emphysema more frequently develops in early and middle adult life. That in old persons is commonly of the type of senile atrophy of the lung. Rapidly developed emphysema, as would be inferred from what has been said regarding hereditary weakness of the lung, is more apt to occur in children, but, as pointed out by Hoffmann, these subjects in many instances make a partial or complete recovery instead of passing on into the chronic form of the affection. As to sex it is probable that women are less often affected only because they are less exposed to exciting causes.

Morbid Anatomy.—The emphysematous lung is excessively large and does not collapse when the chest wall is opened. The anterior margins of the two organs may meet or even overlap, these portions, together with the apices and to a lesser extent the basal margins, being particularly affected. The increased space they occupy is obtained by the displacement forward of the sternum, the more horizontal position of the ribs, and the crowding of the heart to the unaffected side if the lesion be unilateral or downward if bilateral; the diaphragm is also depressed. The costal cartilages are often calcified. The pleura over the emphysematous areas is dry and pale and often contains no pigment; when the pigment is absent in areas only the condition is known, after Virchow, as pulmonary albinism. The affected areas, although not commonly œdematous, pit on pressure, a proof of the loss of elasticity. Congestion is not usually present, and, unless it is, the lung is decidedly paler than normal. The organ is below the average weight and to the palpating finger has a peculiar spongy feel well described by Laennec as that of a pillow of down. Crepitation is lacking in the most emphysematous areas, the contained air readily passing from place to place under advancing pressure. Along the margins may be found prominent bullæ varying in diameter from 0.5 to 2 cm. These are formed by the coalescence of distended vesicles and in contradistinction to the somewhat similar appearing blebs found in interstitial emphysema cannot be made to change their location. When the organ is incised many of these bullæ do not collapse, but remain as distinctly outlined spaces. The increased size of the individual vesicles exposed on the incised surfaces is apparent to the naked eye. The smaller bronchi may also show dilatation.

Morbid Histology.—Microscopically two lesions are conspicuous. The first is atrophy of the vesicular septa which show varied degrees of thinning. Many of them largely disappear, leaving only short ends projecting into the space formed by the coalescence of the alveoli which originally were divided by the septum. In this way the union of a large number of vesicles produce the bullæ previously mentioned. The loss in septal tissue means also a diminution of the vascular field of the lung and consequent imperfect aëration of the blood, this in part explaining the dyspnœa which is one of the prominent symptoms of the disease. The second lesion of importance consists of changes in the elastic tissue. The fibres of this substance lose their normal, wavy outline, become swollen, and often undergo fragmentation. In marked

degrees of the change, elastica as such entirely disappears, only a few granular fragments marking the site of the former fibrils. This is a second factor in the production of dyspnœa, the weakened lung being unable properly to contract and thus increasing the amount of residual air, the tidal air being correspondingly diminished. The bronchi are commonly inflamed and usually show thickening of the walls; the smaller tubes may be dilated. Pigmentary infiltration is commonly slight.

Associated Lesions.—These are hypertrophy or dilatation of the right heart or possibly of the entire organ; atheromatous changes in the pulmonary artery with, in some instances, dilatation of that vessel; changes including pigmentation, atrophy, and fibrosis in the liver, spleen, and kidney depending upon congestion secondary to the obstructive lesion in the lung.

2. **Senile or Small-lunged Emphysema.**—This is a disease affecting old persons, and, although it possesses some of the histological features of emphysema, would more correctly be grouped among the atrophies as senile atrophy of the lung. The chest presents a condition entirely different from that in the type just described. It is small, the ribs are more oblique than usual, and the attached muscles are wasted. The lung is decidedly smaller than the normal organ; it collapses when exposed and not infrequently contains accompanying lesions, as congestion, œdema, or even infarction. As in the preceding type, the inter-vesicular septa are atrophied and broken and the resulting coalescence of numbers of alveoli gives rise to large spaces with remnants of vesicular walls showing on the inner surface. These large bullæ may be so numerous and extensive as to almost entirely constitute the lung. The bronchi are often dilated. The septal atrophy here appears primary, the resulting large spaces being thus produced without the intervention of heightened air pressure.

3. **Compensatory Emphysema.**—This is the form that develops in portions of the lung when other parts are airless and is quite satisfactorily accounted for by the inspiratory theory. It may be temporary in point of duration, as when developing in the unaffected lobules in cases of bronchopneumonia. In such instances it is really a physiological overdistension with stretching of the alveolar walls, which on withdrawal of the cause assume their normal condition. More often, however, it is lasting, the vesicular walls undergoing atrophic changes. The latter type is seen in the lung in cases of new growth, especially of multiple metastatic nodules, between and around tuberculous areas or isolated fibroid patches, and particularly in chronic interstitial pneumonia. In the presence of pleural adhesions the condition also develops.

4. **Acute Vesicular Emphysema.**—This condition clearly should not be placed in the group where long-continued usage still keeps it. It is a functional overdistension of the air vesicles coming on rapidly in cases of acute bronchitis or asphyxia or at times during attacks of angina pectoris or of asthma. Relief or death ensues before the vesicular walls atrophy and consequently the affection is not truly emphysema.

5. **Interstitial Emphysema.**—Interstitial emphysema is characterized by the presence of air in the connective tissue of the lung and is due

usually to the rupture of air vesicles during violent expiratory efforts in coughing, as in whooping cough. The distended vesicles in vesicular emphysema may give way and thus allow the air to reach the abnormal location. The condition is also caused by wounds of the lung from without, as by fractured ribs or other penetrating objects. As pneumothorax may arise from pleural infection by gas-producing bacteria it is possible that their presence in the connective tissue of the lung might cause an interstitial emphysema. This type of emphysema is readily diagnosed postmortem by the presence beneath the pleura of variously sized blebs, sometimes 2 cm. or more in diameter, which by pressure can be made to change their place, thus differing from the stationary bullæ in vesicular emphysema. Rupture of these blebs may produce spontaneous pneumothorax, and when occurring near the root of the lung, air occasionally passes into the mediastinum and even the structures of the neck, giving rise to emphysema of those tissues.

Symptoms.—As the evolution of the disease is slow, its symptoms do not manifest themselves abruptly but are of gradual onset and progressive development. It is not unusual for patients to suffer ill health a long time before distinct evidence of emphysema can be elicited.

One of the chief symptoms is dyspnœa. In the beginning of the disease, before pulmonary distension has become far advanced, it may amount to no more than slight shortness of breath upon exertion, but as the lungs lose more and more of their elasticity and the capillaries in the alveoli become obliterated, it grows constantly worse. In a person suffering from advanced emphysema, inspiration is short and quick, while expiration is much prolonged. This peculiarity in breathing is due to loss of elasticity in the lung, upon which, as is well known, expiration largely depends. When this attribute is lost the air is not expelled from the lungs in a normal manner, all the auxiliary forces of expiration being summoned into play. Even then the result is not complete and a certain excess of residual air remains. When the dyspnœa becomes unusually severe, especially during a paroxysm of asthma or when an exacerbation of bronchitis occurs, the patient will often be found pressing forcibly upon his sides in an endeavor to drive more air out of his lungs. The most characteristic circumstance about the dyspnœa therefore is that it occurs with expiration.

A considerable influence is exerted upon the intensity of the dyspnœa by the degree of severity of the associated bronchitis; thus when exacerbations of the latter occur and the secretion in the tubes becomes more copious, the difficulty of respiration will be augmented, whereas, on the other hand, during periods of comparative freedom from cough and bronchial catarrh only slight dyspnœa is experienced. There is nothing peculiar about the cough. As it is more or less constant, it not only harasses the patient, but saps his strength as well, and moreover hastens the development of cardiac complications. The sputum is that of ordinary chronic bronchial catarrh except in those cases in which asthma is present, when it may contain Charcot-Leyden crystals and Curschmann's spirals.

The heart suffers as well as the lungs, and symptoms of circulatory

disturbance are characteristic of the later stages of the disease. The weakness of respiration, the mechanical effect of the retained air upon the lungs, the paroxysms of coughing, all serve to make aëration of the lungs defective and consequently diminish oxygenation of the blood. This condition is at first shown by blueness of the lips and slight lividity. Upon severe exertion the lividity may become so augmented as to constitute distinct cyanosis, and it is likewise increased when exacerbations of the bronchitis occur.

As more and more bloodvessels in the lungs become obliterated, and as an increasing number of alveoli become distended, the work of the right side of the heart is progressively increased. It undergoes hypertrophy in an endeavor to overcome the resistance with which it has to contend, but sooner or later compensation fails because the destructive process in the lungs is unlimited in its potentiality of development, whereas the heart can only hypertrophy to a certain extent; moreover, the functional disturbances engendered by the pulmonary lesions are so violent as to vanquish the saving effort put forth by the increased cardiac action. Thus it is that compensation fails and the heart dilates. Under these circumstances the dyspnoea and cough become more distressing and the cyanosis more pronounced. Digestive and intestinal disturbances ensue. The liver becomes congested, the extremities swell, and dropsy sometimes occurs. Nutrition suffers and the patient grows weak and emaciated. Hemoptysis and hematemesis sometimes take place; epistaxis, too, is not uncommon when there is much venous congestion. Hemorrhoids also are frequently associated with emphysema, being due to hepatic congestion.

Physical Signs.—The thorax presents marked abnormalities, the anteroposterior diameter being much increased, so that it may equal or even exceed the lateral diameter. It is only in exceptional cases, however, that a tracing obtained with the cyrtometer will show equality of the two diameters. The shoulders are rounded, the curve of the spine increased, the clavicles prominent, and the subclavicular spaces obliterated; the sternum and ribs bulge out anteriorly and the intercostal spaces are widened. These changes give the chest a barrel shape, and make the neck look unusually short. Owing to the cardiac disturbances the superficial veins become dilated and stand out prominently on the skin. They show very plainly in the neck, distension sometimes occurring rhythmically with each expiration, so that they have the appearance of pulsating tumors. Pulsation in the epigastrium is also frequently noticed. Instead of expanding with the act of inspiration the chest becomes elevated and its lower part may even retract when an inspiration is taken.

Palpation will sometimes show that vocal fremitus is diminished, although it frequently happens that no abnormality in this respect is demonstrable. Rarely the apex beat of the heart may be felt in the epigastrium.

The percussion note is increased in resonance, or may even be distinctly tympanitic. The pulmonary area is always increased, often extending posteriorly to the lower costal margin and reaching anteriorly to the level of the sixth or perhaps the seventh rib. The area of cardiac dullness

is greatly diminished and may be entirely obliterated. Even when the heart is enormously hypertrophied it may happen that only a small area of cardiac dulness can be detected owing to the fact that the distended lungs almost entirely cover it.

The diaphragm is at a lower level than in health and the liver dulness often begins in the seventh costal interspace. The area of splenic dulness cannot, as a rule, be well defined owing to the distension of the lung on the corresponding side. The stomach is often dilated, but it cannot always be outlined for the same reason that it is not always possible to make out the boundaries of the spleen.

Upon auscultation the breath sounds are found to be weak. The inspiratory sound is short and labored, the expiratory sound prolonged and feeble. As bronchitis is frequent, rales and rhonchi are often heard in all parts of the chest. A peculiar crepitant sound which has been attributed to friction of the distended portion of the lungs upon the pleura is also sometimes present. The cardiac sounds are feeble owing to the distended lungs overlapping and covering more or less of the heart. As cardiac involvement becomes more pronounced, the signs of tricuspid insufficiency manifest themselves.

Complications.—The distinct complications are pneumothorax and interstitial emphysema. The former results from the rupture of pulmonary vesicles, the latter sometimes follows a violent paroxysm of cough or overexertion.

Diagnosis.—The general appearance of a person suffering with advanced emphysema, together with the symptoms complained of and the signs elicited upon examination of the thorax, usually suffice to prevent the disease from being confounded with other affections. The characteristic dyspnoea, the cyanosis, and the shape of the thorax make a picture which is not formed by any other disease. There is, however, a disease which presents some symptoms and signs common to emphysema, namely, pneumothorax, but its onset is sudden instead of gradual, it is limited to one side of the thorax, and the deformity which stamps emphysema is not present. Further, in emphysema the intercostal spaces are not obliterated as they are in pneumothorax.

Fränkel states that extensive adhesions of the parietal pleura to the lungs may give rise to symptoms closely resembling those of emphysema and cause hypertrophy and dilatation of the right side of the heart. When the entire surface of the pleura is not adherent, the relatively free portions of the lung may become distended. If it happens that only the lower portions are adherent, the upper part of the lungs may become distended and produce alterations in the conformation of the upper part of the thorax. This condition, however, must be exceedingly rare. It would be differentiated from emphysema by the absence of the physical signs relating to the lower part of the pulmonary area. If of long duration, however, the process would amount to the same thing as a moderate degree of emphysema. The symptoms produced by the pressure of tumors upon the trachea and larger bronchi ought not to be mistaken for emphysema, for although dyspnoea is present and the vesicular murmur diminished there is no deformity of the thorax.

Prognosis.—Emphysema is incurable, but much can be done to render the patient comfortable and to prolong his life. Even when left to pursue its course unhampered it is not a rapidly fatal disease; so that persons affected with it often live for years, although their existence is always shortened. Seasonal changes exert a material influence upon the comfort of emphysematous patients and likewise upon the severity of their disease. In winter the bronchitis is more subject to exacerbations than it is in summer, and for this reason patients are often worse during cold weather than at other times of the year. As long as cardiac compensation is maintained there is no immediate danger of death unless some complication sets in, such as bronchopneumonia and influenza. Dropsy and pulmonary hemorrhage are very serious complications.

Treatment.—As emphysema is an incurable malady the efforts of the physician should be particularly directed to preventing its development in those who are predisposed by reason of chronic bronchitis and asthma, and also to delaying, as far as it is in his power, the evolution of the disease when it is detected in its incipient stage. A careful regimen will greatly reduce the liability of the development of emphysema and also materially prolong the days of those who are subject to it.

Persons affected with chronic bronchitis or asthma should take the utmost pains to avoid exposure to cold and dampness, and should be constantly on their guard against sudden changes of temperature. Those whose means permit it should spend the colder months of the year in a warm, sheltered climate at a moderate elevation, such as that of Egypt and the Riviera, or Southern California. If the cough is very dry and expectoration scanty, moist climates are suitable. In summer, residence in localities situated near pine forests is desirable. The altitude must be moderate and not high, and a place should be selected where strong winds do not prevail. The Maine woods and the Adirondack mountains are suitable places for summer residence. During bad weather these persons should not venture out of doors. They should be warmly clad at all times. Occupations demanding great physical exertion should be relinquished, as should also those in whom there is exposure to dust or irritating fumes.

The diet should be substantial, but composed of food that is easily digested. The bowels must be regulated, laxatives being used if necessary. These rules of hygiene also apply to those who are already affected with the disease.

Different mechanical appliances have been employed for the purpose of facilitating the expulsion of air from the lungs. Thus an elastic belt has been worn around the lower part of the thorax, and Strümpell's apparatus, consisting of two boards joined at one end by an elastic band, has been used, one board being placed on each side of the thorax and pressure made during expiration by the patient grasping the anterior ends and bringing them forcibly against the body. A more elaborate apparatus devised by Steinhoff has also been used for the same purpose. Swedish movements, consisting of direct pressure upon the ribs or forcible rotation of the trunk upon its axis alternately from one side

to the other, have been employed for the purpose of immobilizing the ribs, and thus arresting the changes in the configuration of the thorax.

Hydrotherapeutic measures are valuable adjuncts, as they exert a favorable effect upon the heart and circulation. Hot and cold douches, the cold rub, and the cold half-pack have all been used with benefit. They should not be employed as a matter of routine, but should be selected for individual cases as the physician may deem advisable. The hot douche has been used with good result in connection with some of the pneumotherapeutic measures.

Various methods of pneumotherapy have been used, and it has been asserted that brilliant results have followed their employment. The condensed-air bath was highly recommended by Dujardin-Beaumetz, but it is doubtful if any good results follow its use other than those which depend upon its stimulating effects upon the bronchi. The distension of the lungs cannot be influenced by it. For the subjects of advanced cardiac disease and arteriosclerosis it is dangerous.

Expiration into rarefied air has been tried, both alone and in conjunction with the condensed-air bath. It causes retraction of the thorax, and increases the force of expiration, thus causing more air to be expelled. This method seems rational and, indeed, some of its strongest partisans have asserted that most brilliant results have been secured by its employment. That many of the assertions as to its value were extravagant has been proved by further clinical experience and scientific investigation. Temporary relief is afforded in some cases by the inspiration of rarefied air, but in others no benefit is derived.

The inhalation of mineral waters by atomization and vaporization also requires mention. Sulphur and arsenical waters have been extensively used in France for this purpose, and it is stated that relief has often followed their employment. They are inhaled in the form of a fine spray, and are also vaporized. It is not to be doubted that they frequently relieve the symptoms of bronchitis. At Luchon, in France, the inhalation of sulphuretted vapors by the method known as "humage" has been practised, and is said to afford good results. It is not improbable that the regimen of living followed at these resorts, together with the baths and internal use of mineral waters, contribute to bring about a large part of the relief.

Venesection is valuable for the relief of severe dyspnoea and cyanosis. The extraction of a pint of blood will sometimes save a patient who is gasping for breath, and so cyanosed that he is black in the face. Venesection should not be used in any but the most severe cases.

The treatment of the disease by drugs must be directed to combating symptoms as they arise. Bronchitis and asthma must be combated, and circulatory disturbances controlled as much as possible. Exacerbations of the bronchitis are to be treated by the use of expectorants, such as ipecacuanha and small doses of apomorphine, by counterirritants such as turpentine liniment or mustard applied to the chest, and by sedative inhalations such as a mixture composed of equal parts of compound tincture of benzoin and paretoric, of which a tablespoonful is used to the pint of hot water. When there is profuse secretion of mucus

in the bronchi, an emetic dose of apomorphine will sometimes cause its expulsion and afford relief. For the constantly associated chronic bronchitis ammonium chloride is probably as good a drug as we possess. It may be given in 5-grain doses every four hours, and if the cough is very distressing, gr. $\frac{1}{6}$ (0.01 gm.) of codein sulphate or gr. $\frac{1}{12}$ (0.005 gm.) of heroin may be added. This drug may be administered in fluid-extract of licorice or syrup of wild cherry. Terpin hydrate and creosote may sometimes be used with advantage. The thing to be feared about all these expectorants is that they may disorder the stomach. If they do they must be stopped at once.

For an attack of asthma a hypodermic injection of gr. $\frac{1}{4}$ (0.016 gm.) of morphine and gr. $\frac{1}{100}$ (0.0006 gm.) of atropine may be administered, and if the condition of the heart does not contra-indicate it, a few whiffs of amyl nitrite may also be given. For failing cardiac action, digitalis in small doses and strychnine fulfil all indications; 5 drops of tincture of digitalis three times a day will support a failing heart and prolong the patient's comfort for a considerable period. Large doses of strychnine, for instance, gr. $\frac{1}{20}$ (0.003 gm.) three or four times a day, for a short time, not only stimulate the heart, but also exert a similar effect upon the respiratory centre. It is not at all uncommon for marked improvement in the bronchitis to take place under the use of these drugs.

When dilatation of the heart has occurred and venous congestion is marked, larger doses of digitalis are indicated; 10 to 15 minims may be given every four hours, but, of course, the cumulative action of the drug must be borne in mind, and a watch kept for its manifestations. Digitalis is often less efficient in the cardiac disease of emphysema than it is in other forms of heart disease, for the reason that it does not materially influence, and certainly cannot arrest, the lesions in the lungs upon which the heart trouble depends.

The iodides have long been employed in the treatment of emphysema. At one time it was thought that they might prevent destruction of the pulmonary vesicles, but such a theory is not tenable. The good which follows their administration depends upon the effect they exert upon the concomitant bronchitis and upon their action on the bloodvessels. They lower arterial tension and may retard the development of arteriosclerosis. Five grains (0.3 gm.) of the iodide of sodium or ammonium may be given in water or milk after the meals. The syrup of hydriodic acid may be substituted when the ordinary iodides disagree.

GANGRENE OF THE LUNG

Etiology.—Gangrene of the lung is due to partial or entire necrosis of a portion of the organ and added infection which probably always is mixed in character, although in one reported case the *Trichomonas intestinalis* was the only demonstrable cause. Necrosis alone, without the phenomena of gangrene and infection by certain of the bacteria which are often found in gangrenous tissue, does not ordinarily give rise to this process. Studies indicate that the saprophytic putrefactive bacteria are a necessary adjunct to the already necrotic and usually

previously infected tissue, but no special bacterium which in every case acts as the exciting cause has been isolated. As a consequence, gangrene is found in connection with processes that lower the vitality of pulmonary tissue by interfering with the blood supply and which favor, or actually carry with them, infection of the necessary type. Just why gangrene occurs in certain instances and not in others under what appear to be similar circumstances in both is not perfectly clear. Difference in tissue resistance is the most reasonable explanation.

Among the important causes are: (1) Lobar pneumonia. This disease does not often terminate in this manner, Aufrecht meeting with no instance in 1500 cases. It may or may not be preceded by abscess formation. (2) Aspiration pneumonia. In these cases the causative agents are drawn into the finer bronchi where the process begins. (3) Pulmonary embolism. This is most frequently a cause when the emboli are from a septic focus, but the plugging of a large vessel by a non-infected embolus may induce the condition. Infectious thrombosis of the cerebral sinuses is in this way an important cause, abscess of the lung not uncommonly being first induced. Any of the causes mentioned in the consideration of pulmonary infarction, especially if the primary focus be infected, may result in gangrene of the lung. (4) Foreign bodies in the bronchi or bronchiectatic cavities may lead to gangrene. In either case intensely infectious material gathers in the affected area and is propagated into the surrounding tissue. Tuberculous cavities may also act in this manner. (5) Trauma. This may exert its effect in the way of simple contusion of the chest wall or by actual perforation of the wall and direct injury and infection of the lung. (6) Infectious and debilitating diseases, as typhoid fever, diabetes mellitus, and long-continued bronchopneumonia. (7) Suppuration in the lung. (8) Pressure upon the pulmonary vessels by aneurism or new-growths in the lung or in adjacent structures. Gangrene is prone to follow rupture into the lung of cancer originating in contiguous tissues.

Morbid Anatomy.—Gangrene of the lung may be diffuse or circumscribed. The former rarely occurs, but may terminate an attack of croupous pneumonia, affecting, as does that disease, an entire lobe or even a whole lung. Occlusion of a large branch of the pulmonary artery may also induce this type. It corresponds to the so-called spreading gangrene of the extremities in that the gangrenous area possesses no definite line of separation from the surrounding structure, the grayish or dark necrotic area passing gradually into the inflammatory zone of recognizable pulmonary tissue that surrounds it.

Circumscribed gangrene may be in the form of single or multiple foci, but in either instance the diseased tissue is sharply separated from the surrounding lung. The affected area is at first brown or slightly reddish in color, but soon becomes dark and finally almost black, liberated pigment from disintegrating blood cells being largely responsible for the coloration. A greenish tinge may appear, but this is usually not so prominent as in the gangrene of external parts. Softening and disintegration soon occur and a cavity is produced. Unless of large size the cavity is not always entirely empty, but contains one or several

irregular masses of softened and discolored lung tissue which have not entirely liquefied. In the ragged wall or even passing through the cavity may often be found bloodvessels and bronchi which have resisted the necrotic processes. When cavities are formed, the characteristic sputum appears and the odor of pulmonary gangrene; hemorrhage may occur, the vessels in the affected part not usually being firmly thrombosed. Surrounding the inner wall of the cavity is a zone of congested or hyperemic tissue and external to this an œdematous area. Leukocytes appear in the outer zones, and if the gangrenous focus be small and the reparative powers of the living tissue active, connective-tissue formation with healing of the necrotic area may limit the process and lead to recovery of the patient. This unfortunately is not a common occurrence.

Symptoms.—As in the case of pulmonary abscess, so, too, in gangrene, the manner of onset and the symptoms of the disease depend somewhat upon the causes which give rise to its development. Thus when it develops in the course of specific affections, the symptoms of the latter may predominate at first, although pulmonary disturbances may even then be present in lesser degree, for the reason that it is not uncommon for the gangrenous process to be preceded by lobular pneumonia, and moreover because some infiltration is invariably produced in the lung before distinct necrosis takes place. When due to croupous pneumonia, its onset is usually marked by a chill and elevation of temperature some days after crisis has occurred. When cavities in the lung become necrotic the process is usually slow and marked by gradual increase in the severity of the symptoms previously present.

It will be seen, then, that, as a rule, symptoms referable to the respiratory organs, together with some elevation of temperature, loss of appetite, and weakness precede the more characteristic manifestations of gangrene, and that they may continue for days or weeks before the latter become pronounced. Although the onset is not sudden in the sense that the disease attacks persons who were previously in good health, the establishment of the gangrenous process is, however, usually announced by a marked exacerbation of the prodromal symptoms, which is often very abrupt. The temperature rises higher and chills may occur, the cough becomes worse and dyspnoea sometimes ensues. As soon as the necrotic area communicates with a bronchus the sputum undergoes a change. While up to this time it may have possessed the characteristics of pneumonic sputum, contained a little blood, or merely have been such as is expectorated in bronchitis, according to the individual case, it now is found to possess an attribute peculiarly its own. This property is an extremely fetid odor such as is not met with in any other disease, and which has been variously described as resembling that of fecal matter, dung-water, or putrefying flesh. This odor is transmitted to the patient's breath, and is so intense and penetrating that it is often diffused through the air of the entire room.

With the supervention of this sign the subjective symptoms become accentuated. Fever increases, the temperature rising perhaps as high as 104° or higher; the pulse becomes rapid, soft, and compressible; the cough more distressing, and exhaustion greater; any attempt to move

increases the severity of the symptoms. The face is pale and drawn, the tongue dry and cracked, the extremities cold, and the whole body sometimes covered with a cold sweat. Anorexia is complete and vomiting may occur, both being due no doubt to the foulness of the expectoration. Diarrhœa may also be present. It has been observed that the patient is inclined to lie on the affected side, thereby causing gravitation of the secretion and lessening the frequency of expectoration.

The expectoration is usually abundant. When the sputum is first coughed up it is of a dirty gray or brownish color. If it be collected in a glass it will be found to separate into three layers: In the bottom of the glass there is a thick, opaque stratum, of a yellow or greenish-brown tinge, consisting of pus, fragments of lung tissue, and gray or yellow grumous masses. Above this stratum is a transparent layer of serous fluid, perhaps having a few flocculi floating in it, while superimposed upon this is a thick, opaque, frothy layer, of a dirty yellow color. Microscopic examination of the lowest stratum reveals the presence of leukocytes, red cells, epithelium, and elastic tissue. Traube has called attention to the fact that elastic tissue may be absent, and its absence is attributed by Filehne to the action of a bacterial ferment which he discovered, similar to trypsin. The clot-like plugs are found to contain fatty acids.

A special form of pulmonary gangrene which requires mention is that which occurs in diabetes mellitus. Its course is very chronic, lasting perhaps for many months. It usually begins as a pneumonic process with profuse expectoration of blood-stained sputum, which finally becomes malodorous, although it is never so offensive as that in other forms of the disease. Hemorrhages are of frequent occurrence.

Physical Signs.—In the beginning of the disease examination of the thorax fails to reveal distinctive signs. There may be areas in which the percussion note is somewhat impaired, and upon auscultation moist rales and diminution of the breath sounds may be heard. As the morbid process advances and the pneumonic infiltration around it becomes more extensive, dulness may become more pronounced. This is more likely to be the case when the gangrenous area is superficial than when it is deep. As softening of the dead area takes place and the necrosed tissue begins to be expelled, the signs of cavity formation may appear. The rales become larger and more moist and amphoric breathing and pectoriloquy may be heard. Owing to the accumulation of secretion in the tissue around the cavity, subcrepitant rales may be heard in an area beyond its borders. Bronchial breathing may be present, as in some cases extensive consolidation exists around the cavity.

Complications.—The principal complications are hemorrhage, empyema, and metastatic abscesses. Hemorrhage is prone to occur; it is due to involvement of bloodvessels in the gangrenous process. When the latter is situated superficially it may extend to the pleura and cause a portion of the latter structure to slough away, with the result that pyopneumothorax is produced. The pleura may also become inflamed without being ruptured, and the effusion which is poured out is generally purulent. Metastatic cases owe their origin to septic emboli resulting from disintegration of blood clots which form in the vessels of the

lung. They are commonly located in the brain, although they may occur in the liver, spleen, and kidneys. Their presence in the brain gives rise to cortical irritation, to hemiplegia, and to monoplegia.

Diagnosis.—This rests upon the putrid odor of the breath and sputum and the physical characteristics of the latter. The physical signs of cavity alone are of no worth, because they may be produced by other lesions, but when taken in conjunction with the diagnostic points just mentioned they are of corroborative value. The previous condition of the patient and the mode of onset and evolution of his present trouble must be taken into account, especially in those cases where the process is not acute. The degree of prostration will also serve as an index.

In putrid bronchitis the odor of the breath and sputum is not so foul as it is in gangrene, and, moreover, elastic tissue is never expectorated; the constitutional disturbances also are not so severe. It may be very difficult to distinguish between cases of ulcerating tuberculous cavities and gangrene, although the tubercle bacillus may be found in the sputum of the former disease. Tuberculous cavities may, however, become gangrenous, and in this case the bacterial findings are of little value.

Prognosis.—Gangrene of the lungs is a very fatal malady. In the acute form death usually occurs within a few days after the development of the disease. It may result from hemorrhage, acute toxemia, or complications such as pneumothorax or metastatic abscesses. In the subacute and chronic cases the patient may die from exhaustion or sepsis. When the lesion is small and circumscribed recovery may take place.

Treatment.—Little can be expected from medical treatment. The patient's strength should be maintained, if possible, by the use of highly concentrated liquid food, given in small quantities at frequent intervals, with the liberal administration of alcohol. Large doses of quinine and tincture of chloride of iron may be given in the hope that they will combat sepsis, but if the iron disturbs the stomach it must be discontinued. Inhalations of turpentine, creosote, and carbolic acid have been recommended. They may lessen somewhat the terrible stench created by the decomposition going on in the lung, and perhaps soothe the irritated bronchi, but they cannot arrest the gangrenous process. For cough and pain morphine may be given, and it may likewise be administered when hemorrhage occurs.

For subacute or chronic gangrene such as occurs in diabetes or chronic tuberculosis, supportive treatment is indicated, together with the use of stimulating inhalations, such as turpentine or oil of sandalwood. As to surgical treatment, it may be stated, as a rule, that operation is indicated early in every case in which a single limited lesion can be isolated, and the patient's condition is grave. If no alarming symptoms are present a little delay may be tolerated, but in any event the removal of a gangrenous focus would seem to be rational. If the lesion cannot be located, as will happen to the majority of cases, unless pulmonary destruction is extensive, exploratory incision may be made in an attempt to find the sphacelated mass. Empyema demands immediate operation. When small multiple foci are present operation is of no avail.

ABSCESS OF THE LUNG

Etiology.—Abscess of the lung is a term often applied indiscriminately to suppurative conditions of whatever type developing in that organ, although in many of them the lesion does not possess the characters of abscess in other viscera. This is due largely to the anatomical peculiarities of the lung and, although it gives rise to some discrepancy between clinical and pathological descriptions, practically the point is not one of extreme importance. Primary suppuration in the lung almost never occurs and consequently, although pus is found in the organ under varied circumstances, pulmonary abscess, properly so called, develops only in two groups of cases: (1) In areas of previously diseased lung tissue, and (2) as the result of the lodgement of infected emboli. In the former group are a number of conditions. Croupous pneumonia is occasionally followed by suppuration, the resulting abscess being either single and possibly occupying a large part of a lobe, or more often there are multiple smaller foci through the pneumonic area. This type is to be differentiated from a condition arising in pneumonia and commonly known as purulent infiltration, in which during resolution an excess of liquefied exudate macroscopically resembling pus, bathes the pulmonary tissue and gives rise to the name; microscopically and bacteriologically this material in such cases is shown not to be pus. In the nature of trauma with added infection, aspiration and deglutition pneumonias frequently produce suppuration by carrying pyogenic bacteria into the lung with food or other substances. The former is apt to occur after operations upon the mouth, tongue, or throat, or as a sequence of suppurative lesions of the upper respiratory passages. Foreign bodies in the bronchi or lungs may be the cause of suppuration. Puncture of the pleura by an exploring needle or by a fragment of a broken rib or other body may be followed by pulmonary abscess. Emboli from whatever source, bearing pyogenic organisms and lodging in the lung, give rise to the so-called metastatic abscesses. These are usually small, nearly always multiple, and often extend to the pleura as cone-shaped areas, although abscesses may arise without the formation of definite infarcts. If the abscess be superficial, pleurisy develops over it and rupture into the pleural sac is not uncommon, the latter giving rise to empyema or possibly pyopneumothorax.

Other instances of suppuration in the lung, at times designated as pulmonary abscess, are those in which the organ is invaded by pus from contiguous structures. This may occur in localized empyema, from extension into the lung of cancer of neighboring tissues, in suppurative lesions of the mediastinum, and in cases of pus formation in the abdominal cavity, particularly hepatic abscess and suppurating echinococcus cyst of the liver, which reach the lung through the diaphragm. In most of these cases the pus passes through the lung, gains access to a bronchus, and is expectorated instead of increasing locally by peripheral extension of the necrotic process and thus forming a true abscess. Extension by the lymphatics in these cases may, however, give rise to new foci of pus formation. Another form of pulmonary suppuration in the

shape of a diffuse suppurative lymphangitis, peribronchial in location, is sometimes found postmortem, but is unrecognizable during life. In this the pus, which is found in the interstitial structure and larger lymphatic tracts, may be due to infection of the lymphatics by bacteria from the pleura or from the tissues around the root of the lung. Suppuration occurring in a tuberculous cavity as the result of secondary infection is sometimes designated pulmonary abscess.

Morbid Anatomy.—As mentioned in discussing the types of the lesion, abscess of the lung may be large or small, the size of a lobe or 2 cm. or less in diameter. The cavity contains the ordinary constituents of pus and usually in addition fragments of lung tissue and the remains of partially disintegrated alveolar epithelial cells. Fragments of lung in the form of alveolar elastica appearing in the sputum form a valuable aid in diagnosis of abscess. The cavity of the acute abscess is bounded by a wall consisting of an inner layer of necrotic lung tissue containing polynuclear leukocytes, a second zone densely infiltrated with inflammatory products, and possibly containing proliferated connective-tissue cells, and a peripheral zone of œdematous pulmonary tissue. In some cases of high tissue resistance and slow progress of the abscess a limiting wall of new fibrous tissue is formed. If evacuation of the contents is complete, cicatrization of the entire area may take place. Neither of these terminations is common. The wall of a pulmonary abscess may become gangrenous, especially if the pus has been evacuated and the resulting cavity imperfectly drained. If the abscess wall be formed partly by the pleura, as is usual in embolic abscesses, the latter structure will be surmounted by a fibrous exudate in which pus formation may or may not occur.

Symptoms.—The symptoms of suppuration in the lung vary somewhat in accordance with the cause of the development and the size and number of the lesions present. When due to a septic embolus, the course of septicopyemia, or one of the more malignant acute infectious fevers, as variola, symptoms of respiratory disturbance may be masked by the general constitutional manifestations of the disease. In other cases, however, cough, dyspnœa, pain in the chest, and the expectoration of purulent sputum will be superadded to the other manifestations, provided that the patient does not succumb early to his general infection.

Abscesses due to the inspiration of foreign bodies are characterized by a septic temperature, cough, dyspnœa, and pain, a syndrome which may be said to characterize all forms of acute pulmonary suppuration; however, in this class of cases, it supervenes shortly after the foreign substance has lodged in the lung and is not superimposed upon another symptom-complex. It may be that signs of bronchopneumonia have been observed before those of suppuration ensued, although as a rule septic foreign bodies induce pus formation very rapidly.

When suppuration of the lung occurs in lobar pneumonia, its presence will be marked by continuation of the fever beyond the usual duration and failure of the consolidated areas to undergo resolution. The temperature may assume a higher elevation than that at which it was maintained during the course of the disease, but it will usually be

characterized by fluctuations, assuming a distinct septic type with morning remissions and evening exacerbations. Dulness will persist over the affected area and bronchial breathing or indistinct breath sounds will be heard upon auscultation. As the morbid process advances and more tissue undergoes liquefaction, and especially after the abscess begins to empty itself, the signs of cavity in the lung may become apparent; amphoric breathing and coarse crepitant rales may then be heard.

The sputum undergoes important changes, becoming grass-green, or sometimes dark brown in color. As soon as the abscess communicates with a bronchus its contents will begin to be freely discharged. Sometimes a gush of pus, so profuse as to fill the patient's mouth and nearly choke him, will suddenly occur. Fragments of elastic tissue are brought up with the expectorated material. The odor of the expectoration is not so foul as in putrid bronchitis and gangrene of the lung.

Not only do these changes in the objective symptoms take place, but alterations in the subjective symptoms may likewise occur. It not uncommonly happens, when a single large abscess has emptied itself in the manner just described, that the fever subsides and the general condition improves, although pus may be discharged for an indefinite period varying from weeks to months; some abnormality of temperature may also persist. The duration of these symptoms will depend upon the rapidity with which the abscess becomes obliterated.

In another class of cases due to pneumonia, defervescence takes place in the regular manner, but in the course of two or three weeks the patient develops irregular fever, cough, and dyspnoea, and after being ill for some time may either begin to expectorate purulent sputum, or be seized with a violent paroxysm of cough and bring up a considerable quantity of pus. Relief may then follow and healing take place, or the abscess fill again, and similar attacks follow. Sometimes the patient enters upon a period of decline, loses weight, runs a hectic fever, and succumbs to the inroads of sepsis.

The minute abscesses which are occasionally formed seldom produce any symptoms. This is likewise the case with those small areas of suppuration which form around new growths, although they may be responsible for the slight elevations and irregularities of temperature which sometimes occur. These small abscesses are frequently not suspected during life, but are discovered at autopsy. The softening and liquefaction of indurated areas of lung tissue which sometimes occur in chronic interstitial pneumonia or cirrhosis of the lung, does not give rise to the symptoms above described. Acute symptoms are not present, nor is the sputum characterized by the admixture of pure pus.

Complications.—When a pulmonary abscess is superficial, pleurisy almost invariably results and is very apt to be purulent. The abscess may also break through the pleura and cause empyema in this manner or perhaps give rise to pyopneumothorax. Purulent pericarditis and cerebral abscess are also occasional complications. The suppurative process may also terminate in gangrene. In chronic abscess cavities there is danger of hemorrhage taking place from erosion of vessels in the wall. Amyloid disease may supervene in chronic cases.

Diagnosis.—This may be very difficult. Small multiple pyemic abscesses may not produce distinct symptoms because of the violent disturbance caused by the general infection. When one or more large abscesses communicate with a bronchus so that pus gushes up and fragments of lung tissue are expectorated, diagnosis is assured. The finding of elastic tissue is an infallible sign and will remove any doubt which may have previously existed. When defervescence in croupous pneumonia is atypical or retarded, or when chills and irregular fever occur after crisis has taken place, suspicion should at once be aroused as to the possibility of suppuration in the lung. If the sputum undergoes the characteristic changes, the suspicion will be strengthened and probably confirmed in course of time by rupture of the abscess.

The principal conditions with which abscess of the lung might be confounded are bronchiectasis and empyema. The former, although presenting some symptoms common to abscess, such as the expectoration of purulent sputum and hectic temperature, is to be differentiated by the history and absence of elastic tissue in the expectoration.

Inpurulent pleural effusion which has ruptured into the lung the physical signs of the primary disease will usually remain, so that dulness over the posterior pulmonary area increasing from above downward will be present, and the breath sounds over this area will be diminished. In some cases the symptoms and signs of pyopneumothorax supervene.

Diagnosis between an interlobar empyema and a pulmonary abscess which has not communicated with a bronchus is practically impossible, and even after perforation of the one and rupture of the other has occurred there may be nothing by which a differential diagnosis can be made. It may be impossible to distinguish abscess from gangrene affecting a limited area of pulmonary tissue, although offensive odor of the breath and foul-smelling expectoration suggest gangrene.

Prognosis.—Pulmonary abscess is a serious disease, but the prognosis depends in some degree at least upon the cause and upon the size and number of lesions present. Acute multiple abscesses due to septic emboli are always fatal. Abscesses due to foreign bodies are very fatal, while those due to penetrating wounds usually heal readily unless a large area of tissue has been destroyed. In single abscess following croupous pneumonia hope for recovery should always be entertained. If the abscess ruptures, or can be evacuated by surgical intervention there is a fair prospect of recovery. Of course, the longer the abscess cavity persists the greater will be the danger of death from septic poisoning and exhaustion, from amyloid disease, and from hemorrhage due to erosion of vessels in the abscess wall.

Purulent pericarditis, abscess of the brain, and rupture into the pleural cavity render the prognosis more unfavorable. If surgical intervention can be practised at once in the latter occurrence the patient's chances of recovery will probably be increased, but unless operation is done at once, they are certainly diminished.

Treatment.—Medicinal treatment must be directed mainly to sustaining the patient's strength. Alcohol should be given freely. Nutritious

liquid food must also be supplied. Milk, eggs, strong broths, and cocoa are appropriate articles of diet.

Inhalations of carbolic acid have been highly recommended, but it is doubtful if they accomplish any good. In chronic abscess, iron and arsenic in addition to alcoholic stimulants will be found useful. It is in this class of cases, too, that antiseptic inhalations may prove of value. Carbolic acid, creosote, eucalyptol, and benzoin may be tried. For excessive cough small doses of opium or codein are permissible, but care must be taken not to give enough to check the secretions.

In small multiple pyemic abscesses treatment is of no avail. In regard to the surgical treatment of pulmonary abscess, whenever an abscess can be located, and there is reason to believe that other foci of suppuration are not present, pneumotomy should be performed. Although some pneumonic abscesses heal spontaneously after rupture occurs, it seems that they should invariably be opened and drained once they are positively located. By treating them in this manner the patient will be less exposed to such complications as empyema, purulent pericardial effusion, cerebral abscess, and septicopyemia. When due to extension of suppuration processes originating outside the lung, for instance, to rupture of a subphrenic abscess or an empyema, operation is also urgently demanded. So likewise is it when an abscess breaks into the pleural cavity.

NEW GROWTHS OF THE LUNG

Etiology.—The etiology of primary tumors of the lung is enveloped in the mystery which surrounds that of new growths in general. Primary cancer is much more frequent, 3 to 1, in men, and of West's 6 cases of primary sarcoma 5 were in men, the sex in the other case not being stated. This by inference is in harmony with Aufrecht's belief that trauma is of very great etiological importance. In each of his 4 cases of cancer there was a clear history of injury, and he cites similar instances from the experience of others. Workers in cobalt mines appear especially predisposed to pulmonary cancer.

Morbid Anatomy.—This depends largely upon whether the growth is benign or malignant, primary or secondary. In general, primary tumors are much less frequent than secondary, due either to metastasis or to extension from contiguous tissues. In 20,160 autopsies, Wolff found 46 primary tumors of the lung. The primary are commonly unilateral, the secondary bilateral. The latter, when metastatic in origin, are often widely disseminated.

Benign tumors of the lung are very rare. Adenomata originating in the bronchial glands have been found. Of the connective-tissue series, osteoma, chondroma, fibroma, and lipoma are occasionally met; they are usually small and multiple. A true primary osteoma was reported by Virchow, but there seems little doubt that some so designated have been in reality calcific foci in tuberculous or other disease areas. A few cases of primary enchondroma are on record. They are small,

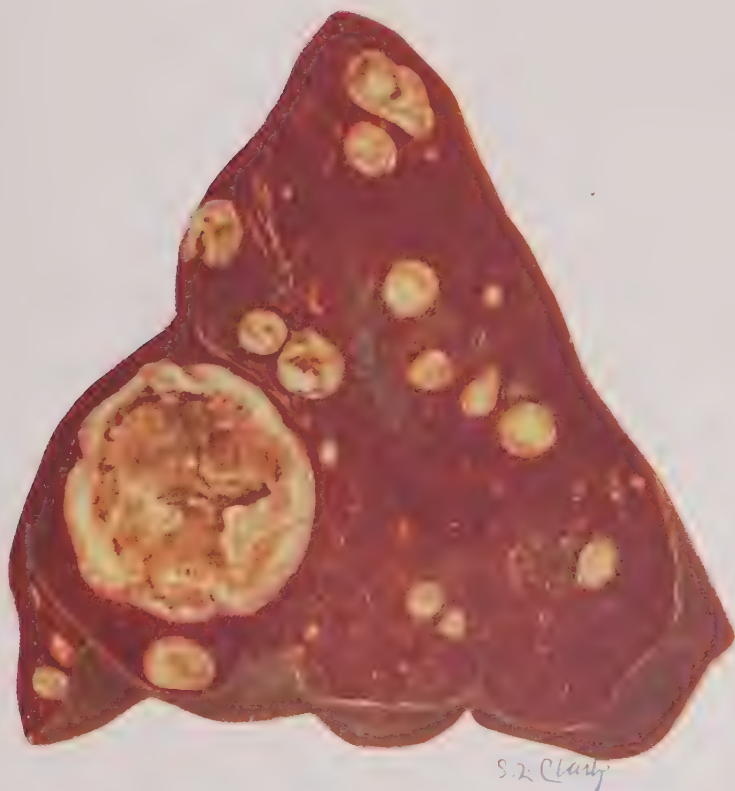
multiple tumors originating from the bronchial cartilages, rarely exceed 1 cm. in diameter, give rise to no symptoms, and consequently are of pathological interest only. Of secondary osteoma and chondroma, 14 cases are on record. Fibroma is rare, as is also lipoma.

Malignant tumors are sarcomas and carcinomas. Among the 330 cases of lung tumor collected by Adler were 211 cancers, 228 sarcomas, and 24 endotheliomas. The *sarcoma* is relatively rare as a primary tumor. Of West's 16 cases of sarcoma of the lung, 6 were primary in that organ. The endothelioma, or sarcoma derived from endothelial cells, is the most common primary malignant connective-tissue tumor. It usually originates in the pleura, but may spring from the lining cells of trabecular lymph spaces or bloodvessels. Of sarcomas secondary in the lung, those originating in bone are the most frequent, a third or more coming from this source. So far as the lung is concerned these tumors do not always conform to the general rule regarding age, and appear more often in adult or advanced life. In some cases there is a long interval between the appearance or removal of the primary tumor and the metastasis in the lung. Prentiss reports a case of removal of a sarcoma of the testicle with symptoms of secondary growth in the lung developing four years later, the patient living another year. Melanotic sarcomas also appear. Possibly belonging to this tumor group is the syncytioma, which occasionally develops in the lung as a secondary growth. Hypernephroma is also a metastatic tumor in the lung and pleura.

Carcinoma is the most frequent tumor of the lung and, while compared with sarcoma, a relatively large proportion are primary, the greater number even of cancers are secondary in origin. The primary is commonly encephaloid in type, although from the anatomy of the lung most secondary growths also, even if from a scirrhus, assume a very cellular structure. West particularly emphasizes the fact, however, that cancer of the root of the lung tends to become excessively fibrous. When primary the tumors may involve most or all of a lobe or an entire lung. Secondary foci may develop by dissemination of the original tumor. Perl, Malassez, Boix, and others, endorsed by Aufrecht, hold that true primary cancers of the lung take origin from the alveolar epithelium. The pulmonary tissue may be invaded, however, by tumors originating in bronchial mucous glands. Primary cancer may remain in the lung or extend to neighboring structures, including the opposite lung. The tumor may appear externally, but extension through the chest wall is not frequent. At times when a bronchus is invaded, the growth extends through the wall and appears as papillary masses projecting into the lumen. In these cases, possibly more often than when the growth is confined to the pulmonary alveoli, fragments or individual cells may be detached and expectorated; a few cases have been diagnosed by finding these in the sputum.

Secondary cancer of the lung is commonly bilateral unless due to extension from contiguous tissues, these including the mediastinum, neck, chest wall, and through the diaphragm from abdominal structures. The possibility of extension from the parietal pleura without the inter-

PLATE XVIII



Secondary Sarcoma of Lung.

vention of adhesions is held by some writers. Metastasis by the lymphatics is a common source of these tumors, but cells are also brought to the lungs by bloodvessels. The latter method may give rise to relatively few small or large nodules in the interior and appearing as bossed or umbilicated elevations beneath the pleura, or to innumerable small, scattered foci; to the latter condition the term carcinosis of the lung has been applied. Cases of extension to the lung through the air passages of squamous epithelioma of the mouth or larynx have been observed.

The effect on the lung of all the varieties of malignant growths is much the same. According to their size they are substituted for a small or large part of the pulmonary tissue and exert pressure on all or a part of the remainder. The latter usually leads to compression and atelectasis of the tissue immediately bordering the tumor nodules, although as a whole the intervening lung, especially if the growth be extensive in the shape of multiple foci, is emphysematous. If the tumor affects a lobe or more as a single large mass, the remainder of the organ is sure to become overdistended. Congestion and possibly added œdema may occur in the pulmonary tissue surrounding the tumor nodules; under these circumstances hemoptysis not infrequently results. Subacute inflammatory changes may also take place in the bordering tissue and in some instances lead to softening; in addition to or independent of this, the tumor itself may soften, the process in either instance resulting in cavity formation. Pressure on the blood and lymph vessels and on the bronchi by tumors at the root of the lung leads to secondary changes, as atrophy, necrosis, œdema, and atelectasis, such as would develop from like interference by other causes. Hydrothorax or pleurisy, the latter either serofibrinous or hemorrhagic, not infrequently complicates cancer or other malignant tumor of the lung.

Symptoms.—The benign tumors may be disregarded because of their rarity and also for the reason that when they are present they may not produce any disturbance. As carcinoma and sarcoma give rise to the same symptoms they may be considered together. When these growths are secondary it sometimes happens that their evolution is so slow and manifestations of malignant disease in other parts of the body so pronounced that evidence of pulmonary involvement is not detected during life, the lesions being discovered only upon autopsy. As a rule, however, especially when the tumors are primary, the disease manifests itself by marked, although by no means distinctive, symptoms consisting primarily of dyspnœa, cough, and expectoration.

Dyspnœa is constant and progressive. At first perhaps only of slight degree or noticeable upon unusual exertion, it gradually becomes worse until in extreme cases it may amount to orthopnœa. It is especially severe in cases in which the neoplasm invades the mediastinum and presses upon the lower portion of the trachea. Interference with the circulatory area of the lung, invasion of the bronchi, and the pleural effusion all contribute to its production, but it is of course most intense when the trachea is compressed. Tumors which grow rapidly naturally produce dyspnœa more quickly than do those whose evolution is more gradual. Cough is variable, depending somewhat upon the size and

location of the growth. Thus when a tumor is so situated as to compress the pneumogastric nerve the cough will be hard and dry, whereas if the tumor is disintegrating, or if an associated pneumonia be present, it will be freer and accompanied by expectoration.

Expectoration is variable both as to its quantity and characteristics. The sputum may remain mucoid or mucopurulent throughout the course of the disease, although it is often blood-stained, and has also been known to be of a bright green color. Sometimes it is coughed up as clear red, homogeneous masses, which have been compared to pieces of currant jelly. There is nothing significant about this sputum; it is merely a homogeneous admixture of mucus and blood, the two being so thoroughly blended that one cannot be distinguished from the other. Sometimes a little pure blood may be coughed up, and if the neoplasm extends into a large air cavity, free hemorrhage may result.

Particles of the tumor itself may also be expectorated. Hampeln has called attention to the presence in the sputum of unpigmented polymorphous cells of different sizes in which both nuclei and nucleoli show plainly. He believes that these cells are pathognomonic of cancer.

Intercostal *pain* is not uncommon, but it may not be so severe as to cause much distress. West mentions a case in which neuralgic pain extended down the inner side of the arm, it being due of course to pressure upon the outer costohumeral nerve. Herpes zoster sometimes runs along the course of a nerve thus compressed. When the pleura is involved intense pain may be a constant symptom. Other symptoms worthy of mention are pain, fever, hemoptysis, dysphagia, interference with phonation, and disturbances of the circulation. Fever is present in some cases, and Fränkel observed it in 19 out of 35 cases. It no doubt is often due to associated suppurative processes in the lung, but it also has been attributed to resorption of the tumor elements.

Pressure of the growth upon the œsophagus causes dysphagia. If the recurrent laryngeal nerves be compressed, disturbances of phonation such as hoarseness, inspiratory stridor, and aphonia will result; pneumogastric compression may cause cardiac disturbance, such as irregularity of the pulse. Pressure upon the sympathetic will give rise to inequality of the pupils and flushing of one side of the face. If the growth encroaches upon the large bloodvessels in the lung, circulatory disturbances will also be produced. If the superior vena cava is involved, symptoms of cerebral congestion are likely to supervene.

In regard to cachexia, it may be stated as a rule that it develops more slowly and is not so pronounced in primary malignant disease of the lungs as it is in other forms of cancer and sarcoma.

Physical Signs.—These depend upon the size and situation and upon the condition of the surrounding pulmonary and other contiguous tissues. Thus, when a considerable area of lung is involved by an extensive infiltrating mass the signs will be different than when only a few small, isolated nodules are present. Again, when bloodvessels are compressed or elevated by the neoplasm, manifestations on the part of the circulatory system will be observed which are absent when the tumor is so situated as not to impinge upon the vessels.

Upon inspection, changes in the shape of the thorax may be noticed. In case there is a large infiltrating growth in the lung the corresponding side of the chest may bulge out and the intercostal spaces be widened. A pleural effusion may also cause bulging. On the other hand, when collapse of the lung has taken place as the result of bronchial occlusion, the thorax may be retracted and its circular measurement considerably diminished. The affected side does not move with respiration.

When the neoplasm presses upon the superior vena cava, considerable distension of the superficial cervical veins will be seen. If the pleura be involved in such a manner that the caliber of the internal mammary vein is diminished, owing to the compression to which it is subjected, the superficial veins of the chest will be unduly filled and stand out prominently under the skin.

Palpation shows that vocal fremitus is normal or exaggerated, according as the growth is localized or diffuse. Percussion elicits variable sounds which depend upon the extent and character of the neoplasm and the condition of the parts around it. In diffuse infiltration of the lung, dullness may be elicited over a considerable area of the thorax. Areas of atelectasis as well as patches of pneumonic infiltrate around a softening and isolated nodule near the periphery of the lung may also give forth a dull note. As a rule, however, isolated nodules in the early stages of their evolution do not cause any changes in the normal percussion note. Sometimes resonance may be slightly impaired or perhaps a hyperresonant note may be obtained. Hyperresonance is often heard when a bronchus becomes obstructed; when a cavity is formed by disintegration of the neoplasm and inflammatory softening of adjacent tissue, an amphoric note will be emitted over the area covering the cavity.

The results of auscultation are likewise variable. In extensive infiltration the breath sounds are much diminished, or may even be absent, being replaced by bronchial breathing. In the nodular form of the disease, however, very slight alterations will be detected. The breath sounds may be somewhat diminished in intensity and perhaps a little rough. Associated pulmonary congestion or œdema, as well as bronchitis, give rise to rales of various kinds. In case a cavity is present cavernous breathing and pectoriloquy may be heard. The cardiac sounds are often abnormally distinct, being transmitted through areas of solidified tissue.

Complications.—The chief complications are pleurisy, pneumonia, gangrene, and atelectasis. The pleura may be attacked by the malignant growth, with the result that it becomes much thickened and indurated. Effusion into the pleural cavity is not at all uncommon when such involvement is present, and the fluid is very likely to be sanguinolent. Rarely, a purulent effusion may be present. Pneumonic consolidation and œdema of the lung are sometimes observed, the latter no doubt is in many instances due to pressure of the growth upon the pulmonary veins, although it may result from stasis in the smaller vessels. Gangrene may ensue either as a result of the destructive process itself or may follow occlusion of bloodvessels by the pressure of the neoplasm upon them. Atelectasis is not at all uncommon, owing to occlusion of the

bronchi. Metastases in other parts of the body—the liver, kidneys, and joints, for instance—sometimes occur. Distinct enlargement of the supraclavicular glands may be noticed.

A very few cases have been reported in which a cancer of the lung has perforated externally, but such an occurrence is exceedingly rare.

Diagnosis.—This may be very difficult if the tumor is small and situated deep in the lung. Even when several such isolated nodules exist, characteristic symptoms may not be manifested and the physical signs may be similar or identical with those observed in other pulmonary disorders. Metastatic growths are very liable to escape attention, especially if they occur late in the course of the primary malignant disease. Pulmonary symptoms associated with emaciation and cachexia, supervening after the removal of a malignant growth in another part of the body would naturally arouse suspicion.

In other cases where the malignant process is extensive and contiguous, and perhaps even remote structures are involved, diagnosis will be readily made. A combination of such characteristic phenomena as dyspnoea unassociated with cardiac disease or severe bronchitis, mediastinal compression, enlargement of the supraclavicular glands, expectoration of currant-jelly sputum, together with the physical signs of pulmonary consolidation or excavation, will leave little or no doubt as to the nature of the affection with which we have to do. The finding of particles of tumor in the sputum would of course make diagnosis positive.

Cases in which there is early involvement of the pleura may be most difficult to recognize. Bulging of the thoracic wall may be caused either by a tumor or by an accumulation of fluid in the pleural cavity, but when it is due to the former cause the tumefaction is apt to be more irregular than when it results from the latter. An encysted empyema, however, might give rise to a localized bulging in the side, and is therefore to be borne in mind. In tumor the dulness may extend from above downward, a condition quite the reverse of that which obtains in pleural effusion. In tumor, moreover, dulness is often not uniform in different parts of the chest, whereas in pleurisy with effusion there is little variation in its degree of intensity unless the patient changes his position.

Thoracentesis affords valuable aid. In some cases the exploring needle may be carried through a much thickened pleura and then fail to withdraw any fluid; this circumstance points strongly to malignant disease, and even though fluid finally be reached the thickening is suggestive of malignancy. If shreds of tissue which adhere to the exploring needle prove to contain carcinomatous or sarcomatous cells, the suspicion will of course be converted into positive knowledge. When fluid is obtained its character may serve to elucidate the nature of the malady. As already stated, in malignant disease it is apt to be hemorrhagic. The presence of a sanguinolent effusion, however, must not of itself be considered conclusive evidence of malignant disease, for it sometimes occurs in tuberculosis and renal disease. The presence of cancerous elements in the effusion is of course conclusive.

Neoplasms of the lung which produce mediastinal compression may give rise to symptoms some of which are identical with those produced

by aneurysm of the aorta. When a tumor is so situated as to elevate the great vessels distinct pulsation may be felt, and circulatory disturbances may also be produced. The most valuable point of differential diagnosis is constituted by the fact that when an aneurysm attains sufficient size to produce symptoms it will form a pulsating tumor directly over or very close to the heart. From this pulsating area a dull percussion note will be emitted. In aneurysm there is no enlargement of the supraclavicular glands, and, moreover, changes in the sputum such as may occur in malignant disease of the lung are not present. The fluoroscopic examination is frequently of great assistance. A new growth does not show the expansile pulsation of an aneurysm.

New growths of the lung may be confused with tuberculosis. Thus when a few small, isolated, primary nodules undergo softening, with the result that cavities are formed and hemorrhage takes place owing to erosion of vessels, the disease may be mistaken for a beginning pulmonary tuberculosis. If it happen that a small hyperresonant area be discovered in the upper anterior region of the thorax, the error is likely to be more firmly fixed in the physician's mind. The presence of fever in such cases lends aid to the mistake, as does likewise the existence of rales produced by inflammation around the area of disintegrating tissue. In such cases the age will afford some assistance. Such hemorrhage occurring in a person past middle life should direct attention to the possibility of cancer or sarcoma. In malignant disease, enlargement of the supraclavicular lymph glands will generally be found, whereas in tuberculosis their size will probably not be increased. Examination of the sputum will in course of time decide the question.

Prognosis.—Malignant disease of the lung is of course incurable. Death may result from asthenia, asphyxia, hemorrhage, gangrene, or oedema. In regard to the duration of life no adequate data are obtainable, for the reason that there is no way of determining at what time the disease begins. Some patients die within a few weeks or months after the first manifestation of symptoms. Others may live for a year or two.

Treatment.—All that can be done is to relieve symptoms and endeavor to sustain the patient's strength. Morphia and cannabis indica should be used freely to control pain. Oxygen may be administered for dyspnoea, but when the latter is excessive and due to compression of the trachea, little good can be expected to follow its use. Operative treatment offers no hope of success. If a primary growth could be recognized early it might be successfully removed, provided it were small and superficially located; but in our present knowledge it is impossible to make a diagnosis sufficiently early to enable us even to entertain any thought of surgical intervention.

CHAPTER XXVIII

DISEASES OF THE PLEURA

By FREDERICK T. LORD, M.D.

PLEURITIS¹

Occurrence.—From the point of view of the pathologist, the occurrence of pleuritis is very frequent. Including simple adhesions with other more marked changes in the pleura, pleuritis was found in 160 (74.4 per cent.) of 215 cases at autopsy (M. G. H.). Such processes pass unheeded or undiagnosed in the great majority of patients, as is shown by the striking disparity between autopsy and clinical reports. Thus, of 18,543 patients admitted to the medical wards of the Massachusetts General Hospital from 1897 to 1906 inclusive, only 460 (2.4 per cent.) are recorded as suffering from pleuritis. Uncomplicated inflammation of the pleura is not a frequent cause of death.

General Etiology.—**Age.**—Pleuritis has been described in the newborn, but is relatively uncommon in infants. Pleuritic effusions in children are more often purulent and metapneumonic in origin, while in adults serous and tuberculous pleuritis is more common. The relation of age differs somewhat between clinical and mortality statistics. Of 760 clinical cases (M. G. H.)² of different forms of pleuritis, about one-third occurred from twenty-one to thirty and more than one-half from twenty-one to forty. In mortality returns, the cases are much more evenly distributed through the different ages, with a larger proportion at the extremes of life.

Sex.—In general, males are much more frequently affected. In the writer's series of 1681 patients with fibrinous, serofibrinous, or purulent pleuritis, 1213 were males, 468 females.

Season.—A similar relation with the seasons obtains in pulmonary and pleural infection. Of 762 patients, 248 (32.5 per cent.) sought the hospital clinic during March, April, or May, the greatest number of cases for any month being 94 in March; while 189 (24.8 per cent.) presented themselves in June, July, or August, 178 (23.3 per cent.) in December, January, or February, and 147 (19.2 per cent.) in September, October, or November.

¹ The statistical data on pleuritis are from three sources: (1) The Massachusetts General Hospital (M. G. H.), Boston; (2) the Presbyterian, and (3) Roosevelt Hospitals, New York. The writer is greatly indebted to W. B. James, of New York, for his kindness in placing much valuable data on diseases of the pleura at his disposal. The M. G. H. data were in great part gathered by C. L. Overlander. The hospital records are rich in data on the cytology of pleural fluids, much of the work on which was done by P. Musgrave.

² Children comprise only a small number of the total admissions.

Bacterial Etiology.—As yet it is impossible to separate the inflammations of the pleura into sharply defined groups according to their bacterial etiology, with a characteristic clinical picture, pathology, course, and termination. The number of different organisms concerned is comparatively small, and in the great majority of cases comprises the tubercle bacillus, the pneumococcus, or the streptococcus. Their limited number is probably due to the relation of the pleura to the deeper parts of the respiratory tract, where mixed infections are less common. The tendency of the tubercle bacillus to invade the subpleural tissue or the thoracic glands in close relation with the pleura is well known and explains its frequent invasion of the pleura.

Classification.—The terms “primary” and “secondary” are convenient for the description of clinical cases, but are somewhat misleading and need a word of explanation. Pleuritis is in reality only very rarely primary, almost always secondary to disease of neighboring organs, especially the lung. When cases are referred to as primary, therefore, it should be understood that the starting point of the disease in other organs has not been detected.

Acute Fibrinous Pleuritis; Fibrinous or Plastic Pleuritis.—The examination of cases with fibrinous pleuritis at the postmortem table shows that small amounts of fluid are usually present. From its clinical importance, however, the group deserves separate consideration.

Etiology.—The cases fall into two principal groups:

1. *Primary.*—This forms the largest division in clinical cases. The disease seldom occurs in perfectly healthy individuals, and some disturbance of the respiratory tract may precede, but more often accompanies, the stitch in the side. In the writer's series, 223 (64.6 per cent.) of 345 cases may be regarded as belonging to this class. Exposure was a possible contributing factor in 30 and alcoholism may have played a part in 19 cases. Undetected pulmonary or other tuberculosis is a probable cause in a considerable but uncertain proportion.

2. *Secondary.*—The disease may be secondary to infective processes in any part of the body. Disease of the lung occupies first place and bronchitis is an important factor. It is probable that small areas of pulmonary invasion, too small to be detected on physical examination, frequently accompany bronchitis, and that bacteria find their way from the peripheral parts of the lung to the pleura. Infection with the tubercle bacillus, especially in the lung or bronchial lymph glands, may be regarded as the starting-point of pleural infection in a large proportion of cases. In this series there was probable or certain pulmonary tuberculosis in 18 (5.2 per cent.), of which 6 showed tubercle bacilli in the sputum. Lobar pneumonia is a frequent cause and is represented by 15 cases. Bronchopneumonia, abscess, gangrene, and bronchiectasis are less frequent causes. Of infections in more remote parts of the body may be mentioned acute or chronic endocarditis, tonsillitis, pyorrhœa alveolaris, arthritis, pericarditis, typhoid fever, and uterine sepsis. Dry pleurisy is not infrequent in the later stages of all chronic diseases accompanied by asthenia and increased susceptibility to infection. Trauma with or without gross injury of the tissues may lead to fibrinous.

pleuritis and usually by infection from the lungs. Pulmonary infarction is an occasional cause, and if the venous thrombosis is latent and hemoptysis does not occur the pleurisy may be regarded as primary.

Relation to Tuberculosis.—The proportion of cases in which the tubercle bacillus is responsible for fibrinous pleuritis cannot be definitely stated. A study of the writer's cases suggests that this form of pleuritis as an apparently primary affection is tuberculous in about the same proportion as in primary serofibrinous pleuritis. This seems to be indicated by the subsequent course. (See Prognosis.) It should be noted, however, that coincident tuberculosis was demonstrated in a smaller proportion of cases of fibrinous (5 per cent.) than of serofibrinous pleuritis (13 per cent.). The tuberculin reaction was less often obtained. Of 12 cases of fibrinous pleuritis in which it was tried a reaction was obtained in 4 (33.3 per cent.), while of 47 patients with serofibrinous pleuritis, in 36 (76.5 per cent.) the test was positive.

Pathology.—The inflamed pleura lacks its normal lustre, is dull, opaque, and coarsely or finely granular, an appearance which can best be seen by scraping the tissue with the knife. It is grayish white, or reddish, and deeper red in places where ecchymoses are present. The membrane is thickened and may reach a centimeter or more in width. The amount of exuded liquid varies. There is practically always more than the normal amount of pleural fluid and this is usually cloudy. The extent of pleural involvement varies from a part to the whole of the pleura. It is not uncommon to find some extension of the inflammation along the interlobular septa in cases with severe fibrinous pleuritis.

On microscopic examination, desquamation and degeneration or absence of epithelial cells are found. The subserous tissue is swollen and contains an increased number of polynuclear cells. Lymph and bloodvessels are widened. The surface of the pleura is the site of a fibrinous layer containing numerous pus cells and serum. With the beginning of resolution the fibrin undergoes fatty metamorphosis and in mild cases may entirely disappear. In more severe inflammations the two layers of pleura become adherent.

Site.—Of 323 cases in which the site of the process was noted in this series it was on the right in 134 patients, in 131 on the left, while the process was limited to the right upper chest in 20, to the left upper in 9. In the remaining 29 cases, a situation at both bases in 7, in the diaphragmatic pleura in 3, and throughout the left side in 1 may be mentioned.

Symptoms.—Prodromata are relatively uncommon. Cough and expectoration, due to respiratory infection, may precede the stitch in the side. In a majority of the cases the onset is sudden, with pain, which varies much in intensity. An initial chill is rare. The temperature is often not elevated and was not above normal in 82 (23.7 per cent.) of 345 cases. A temperature of 99° to 100° or 101° is not uncommon. It may rise to 103° or higher, but high temperature is more often seen in complicated cases. Fever usually gradually subsides within a few days.

Pain.—Pain is an almost constant feature. It may be absent after the acute symptoms have subsided or at the extremes of age. It is often described as sharp, stabbing, or cutting, sometimes dull and dragging.

It is usually circumscribed, rarely diffuse, and is felt in the axillary or mammary region, less commonly in the anterior or posterior lateral and lower parts of the affected chest. It may radiate to the shoulder or lumbar region, less commonly into the upper extremity, the neck or abdomen. The rare cases in which the pain is at first referred to the *abdomen* are troublesome in diagnosis. Of 145 cases in the writer's series this occurred in 8 (5.5 per cent.), and may have been due to diaphragmatic pleurisy. The pain is usually in the upper abdominal region. It may be accompanied by tenderness and muscular spasm and suggest an inflammatory abdominal condition.

The pain of fibrinous pleuritis is usually of moderate intensity, at times almost unbearable, at others slight, and present only with long breath or cough. It may be continuous or intermittent, but is usually most marked at the beginning of the illness, disappearing suddenly or gradually within a week to ten days. In some cases it may last for weeks or months. Movement, laughter, pressure on the affected side, quick change of position, even elevation of the arm, may start or aggravate it. With the advent of pleural effusion, pain diminishes or disappears.

Cough.—This is present in a large proportion; of 145 patients it was noted in 103 (71 per cent.). It was stated to be absent in 18, and the records are silent on this point in 24. It is usually ascribed to pleural irritation, and a relation with this is suggested by the frequency with which forced respiration excites cough, and by its relief when the side is immobilized. It is not improbable that pulmonary infection plays a part in its production, for in 44 cases (30.3 per cent.) expectoration accompanied the cough and rales were noted in 45 (31 per cent.). The sputum lacks characteristic features. It was mucopurulent or purulent in many. In 6 cases it was bloody.

Dyspnœa.—Quick respiration may exist without dyspnœa. When it occurs, dyspnœa is usually slight. It may be due to fever, an effort on the part of the patient to limit the excursion of the lung, because of pain; and if an effusion coexists, it may be due to this.

Physical Signs.—The position, if confined to the bed, is inconstant; at times some relief is afforded by lying on the affected and at other times on the unaffected side. The patient is often more comfortable with the upper part of the spine deflected toward the diseased pleura and the shoulder of that side depressed, from the fixation and compression which this position affords. A diminished expansion and elevation of the involved side can be seen as well as felt, most often in the lower lateral thoracic region. The pulmonary excursion, as shown by percussion of the lower pulmonary margin at the end of inspiration and expiration, and by the amplitude of the diaphragm phenomenon, is usually diminished for both lungs, much diminished or absent on the affected side, and the interspaces are slightly narrower. Percussion may be painful. A change in the percussion note may be determined. The respiratory murmur is diminished but vesicular in character; the vocal fremitus may be diminished, but is usually unchanged.

Pleuritic Friction.—A friction rub can be heard and not infrequently felt as early as twelve to twenty-four hours after the onset. Its occurrence

and resemblance to the creaking of leather did not escape Hippocrates. It is often jerky and may be inconstant, present during one, absent at the next respiration, such irregularity being due to alternate fixation and motion of the visceral against the parietal pleura. It may disappear during the course of the examination. The rub is more distinct during inspiration than expiration. Fibrinous pleuritis may exist without friction sound, and friction does not exclude fluid in a neighboring part of the pleura.

Pseudopleuritic Friction.—Students frequently confuse a sound often heard over the back in normal individuals with pleural friction. This sound is commonly heard during the examination of the posterior thoracic region and while the patient's arms are folded across the chest, each hand resting on the opposite shoulder. It does not usually appear at once and may be present only after two or more minutes of forced respiration. It begins as an inconstant, rumbling, grating sound, at first confined to inspiration, becoming more and more intense and finally occupying both phases of respiration. It may be harsh and hardly to be distinguished by quality alone from pleuritic friction. It varies in intensity in different patients and in the course of the examination of the same patient, ordinarily increasing for a time then gradually fading away. It may then be reproduced after an interval of quiet and heard in subsequent examinations. It is usually bilateral. It may at times be felt with the hand and in some instances is audible several inches from the side. The patient may appreciate it as a grating sensation, but it causes no pain. In the back it is confined to the scapular region, whence it may be followed to a point of maximum intensity over the shoulder-joint. At times it can be heard down the arms as far as the hand as well as along the clavicle. There can be no doubt but that it is due to crepitus at the shoulder-joint. Removal of the hands from the opposite shoulder may abolish it. It is rougher than the sound heard over any contracting muscle of the extremities and is not to be regarded as a muscle sound. It is distinguished from pleuritic friction by its less jerky character, bilateral position over the scapulæ, maximum intensity at the shoulder-joint, disappearance on shifting the arms, and the absence of pain.

Pleuropericardial Friction.—This is not infrequent and often difficult of interpretation. It may be due to inflammation of the pulmonary, costal, or that part of the mediastinal pleura overlying the heart. It is likely to be influenced by the movement of the heart as well as by respiration. Owing to the variable line of reflection of the left costal pleura over the cardiac region, a distinction between pericardial and extra-pericardial friction cannot always be safely made from its situation alone, but in general it may be said that pleuropericardial friction is uncommon over the superficial cardiac dulness, and is usually heard outside this region. It is influenced more than pericardial friction by the respiratory movements. If the patient stops breathing, the friction sound may diminish or disappear.

Pseudopleural Intrapulmonary Sounds.—Loud, sonorous rales may occasionally simulate pleural friction. Their less jerky character and disappearance after cough may suggest their pulmonary origin.

Pleural Crepitation.—At times with symptoms of pleuritis, fine, inspiratory crepitations are heard over the site of the suspected process. These may be pleural in origin, but can hardly be differentiated from intrapulmonary rales.

Blood.—*White Cells.*—Fibrinous pleuritis is more often accompanied by leukocytosis than serofibrinous pleuritis; of 48 cases of primary, fibrinous pleuritis, the white count was 12,000 or over in 19 (39.5 per cent.).

Sequelæ.—Of 345 cases in the writer's series pleural fluid was discovered as a sequence of the process in 5.

Diagnosis.—This is usually easily made from the presence of a friction rub. Cases with an acute onset, with cough and stitch in the side, aggravated by respiration, are due to pleuritis in a large proportion of the cases, even if no friction rub can be heard. The diagnosis of diaphragmatic pleurisy is often troublesome and may remain in doubt for several days. Cases in which pain along the lower thoracic margin is the only symptom are most difficult of diagnosis. To judge from the remarkable frequency with which there is postmortem indication of previous disease of the pleura, it is probable that an undetected pleurisy is the cause in a large proportion of the cases. Rarely the pain is the precursor of herpes zoster. Pulmonary embolism from venous thrombosis should always be considered as a possible cause of an apparently primary dry pleurisy. Phlebitis of the veins of the extremities is not always manifest and the embolus may come from a pelvic, abdominal, or thoracic vein. The possibility of spinal disease must be borne in mind. Tertiary syphilis and tumor are to be considered. Lead poisoning, caries of the ribs, periostitis, and thoracic aneurysm should be excluded. The x-rays may help in the diagnosis. A diagnosis of pleurodynia or intercostal neuralgia amounts to a confession of ignorance concerning the cause of the process.

In typical cases there is little danger of confusion, but the signs may be those of thickened pleura: dulness, diminished vesicular breathing, with preservation of the fremitus, even a friction rub, and yet fluid may be present. The fluid may exist between lung and diaphragm, where small amounts are likely to collect first, and rise little above the pulmonary margin between lung and chest wall. In other cases there may be evidence of thickened pleura and oftenest in the lower anterior aspect of the chest, with fluid in the posterior inferior thoracic region. Again, fluid may be encapsulated and fibrinous pleuritis with friction coexist. In doubtful cases an exploratory puncture must be made. Cases with complicating pulmonary disease are likely to cause most difficulty in diagnosis.

Prognosis.—The immediate outlook is good. The more remote prospects are less favorable. Of 82 cases of primary dry pleurisy in the writer's series, 60 have been followed since their discharge from the hospital. Of these, 18 (30 per cent.), certainly or probably, developed tuberculosis. The patients have been followed from one to twelve years, the average interval being four or five years. The outcome of primary dry pleuritis is thus nearly or quite as bad as that of primary

serofibrinous effusion. The prognosis of the secondary form is that of the underlying cause. Pain may persist after the attack; 15 patients (25 per cent.) complain of occasional or persistent pain.

Treatment.—The immediate indication is the relief of pain, on which the cough and dyspnoea largely depend. *Rest* is the first consideration. In all cases in which there is fever or severe pain, the patient should be in bed. Even in mild attacks, rest shortens the duration and may prevent extension or the occurrence of an effusion. *Fixation* of the side limits the play of the pulmonary against the parietal pleura and may produce immediate relief. It may be accomplished with adhesive plaster. The plaster should not be allowed to remain longer than a week to ten days, and care taken in its removal not to cause abrasion of the skin. A tight thoracic swathe, with shoulder straps, has the advantage of ready removal for physical examination, and does not lead to irritation or infection of the skin. It is to be preferred for patients in bed. In some cases, perhaps from diaphragmatic involvement, fixation of the thorax fails to give relief. In such cases an ice-bag or hot-water bottle may be efficient. If these means fail, a hypodermic injection of morphia may be given.

A possible source of infection should be sought, and if found in any part of the body, should receive appropriate treatment. The occurrence of dry pleuritis should always suggest the possibility of tuberculosis. All primary cases, even the mildest forms in patients otherwise in apparent health, should be treated as if tuberculous until they can be proved to be due to another cause. Careful examination of the lungs, the sputum, and the use of tuberculin may furnish positive or suggestive evidence. Oversight of the patient should not cease with the subsidence of symptoms.

Acute Serofibrinous Pleuritis.—Etiology.—Serofibrinous effusions arising from inflammation of the pleural sac may be divided into three principal groups: (1) *Tuberculous pleuritis* comprises the largest and most important division. (2) *Infectious (non-tuberculous) pleuritis* stands next in frequency. (3) *Other causes* are relatively infrequent and often difficult to group. They are the product of more than one factor, such as general hydremia or venous stasis, on which an inflammatory process is superimposed.

1. *Tuberculous Pleuritis.*—It is remarkable in how many cases serofibrinous pleuritis is apparently *primary* without evidence of disease in other organs. Thus of 1185 cases the disease of the pleura was unassociated with positive findings elsewhere in 750 (63.4 per cent.). The pleural disease was combined with suggestive or positive evidence of pulmonary or other tuberculosis in 160 (13.5 per cent.). The lung was the most frequent site of tuberculosis in this group with 149 cases, of which 47 showed tubercle bacilli in the sputum. There is good reason to believe that a large proportion of cases of serofibrinous effusion, more especially the primary cases and those secondary to pulmonary tuberculous lesions, are due to tuberculosis. This point of view is largely the result of recent investigations and is based on the following:

(a) *Tuberculosis of Other Organs.*—In Osler's 195 cases, 30 showed tubercle bacilli in the sputum. As a symptom of pulmonary tuberculosis

pleural effusion usually comes early if at all. Dense pleural adhesions commonly obliterate parts or the whole of the pleural sac in an advanced stage of the disease. (b) *The Subsequent History*.—This shows that from 35 to 40 per cent. develop manifest pulmonary or other tuberculosis within about six years (Hedges, Sokolowski, V. Y. Bowditch, and others). (c) *Postmortem Evidence*.—Of 131 cases of different types of pleuritis examined postmortem by Osler, 32 were found to be definitely tuberculous. (d) *The Tuberculin Reaction*.—This is positive in a large proportion of the cases. In the writer's series (M. G. II.) tuberculin was given in 47; 36 (76.5 per cent.) gave a positive reaction. A positive result merely means tuberculosis somewhere, not necessarily in the pleura. (e) *The Character of the Exudate*.—The evidence is based on the character of the cells, the demonstration of tubercle bacilli in the fluid, and the results of animal inoculation. *Character of the Cells*.—Lymphocytes predominate in a large proportion of serofibrinous fluids from patients with primary pleurisy with effusion. Excess of lymphocytes is not invariably proof of a tuberculous pleurisy.

Tubercle Bacillus in the Fluid.—The effort to cultivate tubercle bacilli from serous effusions practically always fails. Simple microscopic examination likewise is usually unsuccessful. In primary cases, Jousset claimed by means of inoscopy to have found tubercle bacilli in 23 cases (100 per cent.), but other observers have failed to confirm his results. In 115 cases at the Massachusetts General Hospital in which tubercle bacilli were sought in the fluid, they were found in 24 (20.8 per cent.). Zebrowski,¹ by simple sedimentation of a large quantity of fluid, prevented from coagulation by the addition of sodium fluoride, found bacilli in 12 (55 per cent.) of 22 primary cases and in 10 (83 per cent.) of 12 secondary effusions.

Animal Inoculation.—The most convincing proof rests on animal inoculation. Of 66 cases in the writer's series the results were positive in 15 (22.7 per cent.). Much more striking success is obtained by using large quantities of fluid. Eichhorst, with 15 cc., demonstrated tuberculosis in more than 62 per cent. Le Damany has been most successful, and his use of large amounts of fluid, from 10 to 50 and sometimes as much as 300 cc., led to positive results in all but 8 of 55 cases, while in 4 of the 8 negative cases coincident lesions indicated their tuberculous origin. By the presence of tubercle bacilli in the sputum, in the fluid by animal inoculation or inoscopy, or by operation, Musgrave proved the tuberculous character of 28 (54.9 per cent.) of 51 primary or secondary effusions.

There can be no doubt that tuberculosis occupies first place in the etiology of pleural effusions in any large series of cases.

2. *Infectious (Non-tuberculous) Pleuritis*.—Infection of the pleura with other organisms is capable of causing serofibrinous effusion. The pneumococcus is the most frequent cause in this group. The streptococcus and other organisms may likewise be a cause. A difficulty lies in the exclusion of the tubercle bacillus as a mixed infection.

¹ *Deut. med. Woch.*, 1905, No. 36,

(a) *Metapneumonic Pleuritis*.—This is a well-defined group and represented by 62 (5.2 per cent.) of 1185 cases with serofibrinous effusion. Small effusions of a serofibrinous or purulent character are common in lobar pneumonia. Maragliano demonstrated serofibrinous or purulent effusion in 38 of 58 cases, by means of exploratory puncture. If small amounts are included, a serofibrinous is more common than a purulent exudate. Of 154 autopsies on cases with lobar pneumonia (M. G. H.), a pleural effusion was present in 57, and in these the fluid was cloudy in 30, clear in 10, purulent in 9, and hemorrhagic in 6. The largest amount at autopsy was 500 cc. Tuberculosis was a probable cause of the effusion in one.

(b) *Rheumatism*.—This was coincident with pleuritis with effusion in 13 cases (0.9 per cent.). There is no proof that the rheumatic poison can alone infect the pleura, and it seems misleading to speak of a rheumatic pleuritis to designate a pleuritis with or without arthritic symptoms, in which a favorable result is obtained following the administration of salicylic acid preparations. Until proof can be offered that rheumatic fever is due to a specific organism, and this can be demonstrated in pleural effusions as a cause, it is better for clinical purposes to regard such effusions as complicate arthritis as only possibly rheumatic in origin. As in other forms of pleuritis, tuberculosis must be excluded.

(c) *Trauma*.—Serofibrinous effusion followed trauma in 10 cases (0.8 per cent.). The effusion may be due to simple infection or to tuberculosis.

(d) *Typhoid Fever*.—The association of serofibrinous effusion and typhoid is rare, occurring in only 7 cases (0.5 per cent.) in this series. Among 1500 cases of typhoid, McCrae noted only 3 with serous effusion. The bacilli have been obtained in pure culture from the fluid. Pleural effusions in the course of typhoid fever may also be hemorrhagic, but are most commonly purulent. The complication may occur early, as in Fernet's case, but is more often found during the course of the disease. It is not certain that the typhoid bacillus alone is capable of causing serofibrinous effusion. General infection with typhoid bacilli is so common in typhoid fever that the mere presence of typhoid bacilli in the exudate does not suffice to establish the independence of typhoid pleuritis. The agency of other organisms, and especially the tubercle bacillus, must be rigorously excluded.

(e) *Infection in any part of the body* may be a cause of serofibrinous pleuritis, although the effusion accompanying septic processes is more often purulent in character or becomes so after passing through a serofibrinous stage. Pulmonary infection resulting in bronchopneumonia, pulmonary infarction, pericarditis, malignant endocarditis, uterine sepsis, etc., may lead to serofibrinous pleuritis. In such cases the serous rather than the purulent character of the effusion may be due to the small number or diminished virulence of the infecting organisms or to increased resistance on the part of the patient.

3. *Other Causes*.—A sharp, dividing line cannot always be drawn between transudates and exudates. An inflammatory process may readily be superadded to a transudate and thus complicate the differentiation.

Pathology.—1. *Pleura.*—The appearance of the pleura does not usually differ from that in simple fibrinous pleuritis. The fluid commonly occupies the most inferior parts of the cavity, and in acute cases the fibrinous layers on the two pleuræ are usually easily separated where they lie together above the fluid. Bands of adhesions may traverse the fluid and connect the visceral and parietal layers. In the more chronic cases the two pleuræ may be more or less firmly united above the fluid. It is less common to observe encapsulation of serofibrinous than of purulent fluid. Sacculated exudates are most common at the posterior and inferior aspect of the pleural sac. Rarely more than one encapsulation occurs, and the contents of the two may vary, in one serous, in the other purulent fluid. Miliary tubercles may occur in the pleura without fluid or fibrinous exudate. In the gross appearance the pleura may not differ from that seen in the simple form, and tubercles may be discovered only on microscopic examination.

2. *Side Affected.*—Of 1085 clinical cases in the writer's series the effusion was confined to the left side in 570, to the right in 487, while both were involved in 28. In one the effusion was sacculated on the left, posteriorly, near the spinal column, over an area eight inches in diameter.

3. *The Effusion.*—This is quite variable in its character. It may be largely serous, with only a small amount of scattered fibrinous flocculi. The fibrin may exist as wavy, skein-like masses in suspension, or as more compact, whitish, coarse, membranous shreds or curd-like deposits. A clot usually forms in a variable but short period after evacuation, and may be found as a small, jelly-like mass at the bottom, or may comprise almost the whole volume of the fluid, with only a thin layer of clear serum about it. The fluid is usually amber colored, with an admixture of greenish or reddish from the presence of blood. It may be brownish on removal or turn so after standing. When mixed with considerable amounts of blood it may be blood red, and, if removed after having long remained in the chest, may be darker, even chocolate colored. With jaundice the fluid is more deeply colored and responds to the tests for biliary substances. Most fluids are clear or only slightly opalescent from the presence of albumin in fine subdivision, fibrin in the form of flocculi, clot, fat, or cellular elements. No sharp dividing line can be drawn between serofibrinous fluids cloudy from the presence of numerous cells and those with more or less frank admixture of pus. Cellular elements tend to sediment within as well as outside the chest, and an abundance of polynuclear cells obtained on tapping the upper layers of a pleural fluid may be associated with a sediment of pus at the bottom.

(a) *The amount* is very variable. In acute fibrinous pleuritis there is practically always more than the normal amount of fluid in the pleural sac. Even when the process is confined to the upper parts of the pleura, small amounts are often found at the bases. In 500 cases in this series the amount varied from a few to 4620 cc., the largest measured amount at any one tapping. The right chest is more capacious than the left and larger amounts are likely to be present in men than in women.

(b) *Specific Gravity.*—The determination of this is of great value in differentiating exudates from transudates. It is surprising with what

constancy inflammatory fluids have a specific gravity of 1018 or over. Of 224 cases only 19 had a specific gravity below 1018. It has been shown that the amount of salts and extractives is very nearly the same (Runeberg, Méhu, Reuss, Hoffman) in fluids of different origin, and after the removal of albumin, amount to about 1.08 per cent. in non-inflammatory fluids and to about 1.18 per cent. in inflammatory fluids. A variation in the specific gravity is dependent for the most part on differences in the amount of albumin.

(c) *Albumin*.—This exists in the form of serum albumin, serum globulin, and fibrinogen, to which, if present in sufficient amount, is due the property of spontaneous coagulation. Inflammatory fluids contain a relatively large amount of albumin and fibrinogen. In general, exudates contain 4 per cent. or more of albumin. *Nucleo-albumin* may be demonstrated by the addition of a drop of the fluid to be tested to a dilute solution of acetic acid (2 drops glacial acetic to 200 cc. water). The substance, the identity of which is uncertain, is demonstrated by marked turbidity of the fluid in exudates and very slight or no change in transudates. It is somewhat soluble in an excess of acetic acid and completely soluble in alkalis.

(d) *Fat, uric acid, cholesterin, glucose, biliary acids, and pigments* are occasionally found.

(e) *Cellular Elements*.—The sediment obtained after standing or sedimentation shows red-blood corpuscles, polynuclear leukocytes, small mononuclears (lymphocytes), and endothelial cells. Eosinophiles and mononuclear cells intermediate between the small lymphocyte and endothelial cell are common, but usually comprise only a small proportion of the total number. An occasional mast cell is not an infrequent finding. *Cytology* is further considered on page 1030.

4. *Intrapleural Tension*.—With small effusions this may still be negative. As the fluid increases in amount the tension rises and becomes positive after the pulmonary elasticity is spent. Various factors influence the pressure. It may be relatively high with a small amount of fluid if pulmonary retraction is prevented by pleural adhesions, by pulmonary or mediastinal disease. Pitres¹ finds that the pressure may vary from 0 to +2 or +3 with less than 1000 cc., from +8 to +22 with 1000 to 2000 cc., and from +20 to +48 mm. Hg. with more than 2000 cc. The pressure fluctuates with the phases of respiration. An initial positive pressure may fall during deep inspiration to -40, as noted by Schreiber.² After aspiration the fall may be greater and with deep inspiration even to -90 mm. Hg. The fluid is also under a pressure of its own fluid column and the tension thus varies at different levels.

5. *Mechanical Effects of the Exudate*.—With small effusions the lung contracts and becomes atelectatic. With large effusions it is compressed, completely emptied of air, and for the most part of blood, and may be found as a brown mass, not larger than the closed fist, lying against the spinal column in the upper and posterior part of the affected side. In the absence of long-standing and extensive inflammatory changes

¹ *Arch. clin. de Bordeaux*, 1896, 5, p. 70.

² *Deut. Arch. f. klin. Med.*, 1883, xxxiii, 485.

it is still capable of reëxpansion after removal of the fluid. Under less favorable circumstances, extensive adhesions, the formation of dense connective tissue on its surface and within its substance may prevent this. Such a result is much less common with serofibrinous than with purulent exudates, and since it has become the custom to tap early.

In consequence of diminished negative pressure within the thorax, the *intercostal spaces* show less than their normal depression. Early in the disease they may be narrowed from spasm of the intercostal muscles. With large effusion and increase in size of the affected side the spaces may actually be widened from pressure, and perhaps, also, from paralysis of the intercostals. Later, following the absorption or removal of fluid, the thoracic wall may be depressed, and the intercostal spaces narrowed from contraction of scar tissue. The diaphragm, and with it the liver or spleen, is at first depressed from the loss of the normal negative intrathoracic pressure. With large effusion, the diaphragm is forced downward by positive pressure from above and the weight of the superimposed fluid. The dislocation of the mediastinum and the heart from small effusions is a result of a disturbance of equilibrium between the two pleural sacs. It is dislocated by positive pressure with large effusions. Pressure on the œsophagus may lead to dysphagia, and pressure on or invasion of the region about the vagus, to recurrent laryngeal paralysis.

6. *Absorption*.—Various factors probably play a part in absorption. Hydremic and congestive transudates are rapidly absorbed under favorable conditions. Inflammatory fluids containing relatively few formed elements and fibrin may likewise spontaneously disappear. Purulent fluids, however, may remain indefinitely unless evacuated by perforation or operation. Large effusions are less often absorbed. The mechanism is probably largely mechanical. Small, serous effusions, unassociated with fibrinous obstruction of pleural lymphatics, and interfering relatively little with respiratory changes of intrapleural pressure, are most favorable for absorption, while the opposite obtains in large and inflammatory fluids. West¹ refers to the "lymphatic pump," the action of which is suspended by fibrin plugging the pleural stomata and large effusions which prevent expiration on the affected side. It is probable that osmosis, also, is a factor.

Symptoms.—1. *Primary Form*.—Prodromas are uncommon. Slight cough and failing health may precede the onset. An initial chill is rare; chilliness is common. The disease began gradually in more than one-half (60 per cent.) of the writer's series. There is malaise, pain of variable intensity, fever, and cough. Sudden onset, in which the patient's activity is abruptly interrupted, is less common. In exceptional cases the initial features may suggest pneumonia. There is chill, fever, and severe pain in the side, but no rusty sputum. An insidious onset, especially at the extremes of age, is not infrequent. In a small proportion the symptoms are sufficiently characteristic to suggest the diagnosis from the history of initial pain, which gradually diminishes or stops as the fluid accumu-

¹ *Lancet*, March 25, 1905.

lates and the dyspnoea increases. The temperature may gradually rise as long as the fluid increases, is continuous during this period, intermittent with the effusion at a standstill, and often absent during absorption. It may reach normal at the end of a week or ten days, although continuous or irregular fever may last for a much longer period. The exudate may be discovered by the third or fourth day, if untapped, may gradually increase during the next ten days, then gradually diminish, to disappear in favorable cases during the third, fourth, or fifth week. The disease is often atypical. General symptoms and fever may predominate, and, aside from the pulmonary findings, typhoid fever may be suggested. Pain in the abdomen, with muscular spasm and tenderness, may mislead the observer into the diagnosis of an acute abdominal affection. Both onset and course may be latent or sudden, severe, even rapidly fatal (pleuritis acutissima). There may be an initial chill, rapid rise of temperature, intense dyspnoea, cyanosis, rapid pulse and respiration, delirium, and death in a few days with symptoms of suffocation. An immediate resort to evacuation may be life-saving in such cases.

2. *Secondary Form.*—The onset and course are often so masked by the existing disease that symptoms referable to the pleura are unnoticed or absent. The presence of pleural effusion may then be discovered only during a routine physical examination, or, if this is neglected and the disease is fatal, at autopsy. The presence or absence of symptoms largely depends on the mildness or severity of the primary disease. In pulmonary tuberculosis, however, the symptoms may be typical, since effusion usually occurs early, if at all, in its course, from the frequent obliteration of the pleural sac by adhesions in the more advanced stages. In lobar pneumonia, typical symptoms of effusion are usually lacking or only with difficulty differentiated from those due to the pneumonia itself. There may be an accession of pain, dyspnoea, of cough. The respirations, pulse, and temperature may rise above their previous level. A failure of the temperature to drop at the expected time may be the first indication.

3. *Special Symptoms.*—*Pain.*—This is usually one of the first and most typical symptoms. It was present in 89 of 100 cases of primary serofibrinous effusion in this series. It may be absent, as in 5 cases. Associated tenderness over the inflamed pleura is frequent.

Cough.—This is probably next in frequency, occurring in 83 per cent., absent in 12 per cent., and not given in 5 per cent. It is usually short and dry, but may be accompanied by expectoration (48 per cent.). The sputum is mucoid or mucopurulent; rarely it may contain blood (2 per cent.). Cough alone may be due to pleural irritation. Expectoration should suggest a pulmonary complication, usually an infection, more rarely oedema, evidence of which may be furnished by the sputum.

Respiration.—Short, quick respiration is frequent in the early stages from pain and spasm of the respiratory muscles. The rate may be elevated from fever, encroachment on the thoracic space by fluid, associated pulmonary disease, or embarrassment of the circulation from pressure. The normal relation between the rate of respiration and pulse is much more often maintained with pleural effusion than with pneu-

monia. Quick respiration is more often observed at the onset and after exertion. When the patient is at rest and the exudate has gradually accumulated, one side of the chest may contain its full capacity of fluid without disturbance of the normal respiration-pulse ratio.

Dyspnœa.—The embarrassment of respiration may amount to dyspnœa. This is more frequent in rapidly formed and large accumulations, and may become orthopnœa. At times, however, with small effusions and much limitation of respiratory motion, there may be marked dyspnœa. Cyanosis, with or without turgescence of the cervical veins, is likely to accompany marked interference with respiration.

Temperature.—There is no typical fever curve. The temperature is more often elevated and in general reaches a higher level than with dry pleurisy. Of 100 primary cases in the writer's series, only 10 were without fever. From 100° to 102° is an average pyrexia. In rare instances the temperature may reach 104° to 105° or higher. It is likely to be high in children and robust patients. Absence of fever is occasionally observed in old or debilitated patients and in terminal infections, when the temperature may be subnormal.

Pulse.—The rate usually corresponds to the fever curve. The rapid accumulation of a large amount of fluid may embarrass the circulation and cause a rapid and feeble pulse.

Febrile or Toxic Symptoms.—These are not especially characteristic and are such as may be seen in other infectious processes. At the onset there may be headache, insomnia, malaise, and general pains. The skin is hot and dry. As the fever drops, there may be sweating, which may become a prominent symptom if the process is long continued. There may be thirst, anorexia, even nausea and vomiting, but gastric disturbances are uncommon. In protracted cases the loss of strength and weight may be marked.

Hoarseness may be due to pressure on or paralysis of the recurrent laryngeal nerve. *Dysphagia* from pressure on the œsophagus may be present. Ferber has observed that the passage of food through the œsophageal foramen may be accompanied by pain, when there is diaphragmatic pleurisy. *Singultus* is a rare and interesting symptom. It may be most distressing when the diaphragm is involved.

Urine.—During the acute stage, the urine is small in amount, of high color and specific gravity, with an increase of urea and uric acid and a diminution in chlorides. During absorption, the amount may rise rapidly with an increase in the output of chlorides, the so-called "chlorine crisis," while urea and uric acid are diminished. Traces of albumin and a few hyaline casts may be present and can be ascribed to fever, toxemia, or rarely to stasis.

Physical Signs.—Small amounts of fluid collect in the most dependent part of the thoracic cavity, in the costophrenic sinus posteriorly, and in the region between lung and diaphragm. Until the amount becomes considerable, it intervenes very little between lung and chest wall. In Garland's experiments there was scarcely a trace of a rim of fluid between the lower border of the lung and the chest wall, with injections which occupied less than one-third of the thoracic cavity. In explanation of

this it is assumed that there is a greater elastic traction in the lower than in the upper parts of the lung. Larger amounts finally intervene between lung and chest wall. In favorable and uncomplicated cases, 250 cc. of fluid in an adult should not escape detection. In infants 100 cc. may be discovered.

Inspection.—Herpes is uncommon. Inspiratory dilatation of the *alæ nasi* is less frequent than with pneumonia. The position of the patient is variable. If there is dyspnoea, the patient may be more comfortable sitting upright, from the greater mechanical advantage and from the removal of the weight of the effusion on the lung which this position affords. With small effusions, without orthopnoea, the patient may be more comfortable on the unaffected side. The explanation of this is not clear. Traube has assumed it to be due to the relief of pain from removal of pressure on sensitive nerves in the affected pleura. With large effusions, the patient usually chooses a position on the affected side, thus allowing the sound lung full play and diminishing pressure on the mediastinum. It is not uncommon, even with large effusions, to find the patient lying comfortably on the back. At times an ambulant patient presents himself with a large effusion.

In the early stages of the disease, when there is pain and only a small amount of fluid, the appearance of the thorax does not differ from that described under Fibrinous Pleuritis. With increase in the amount of pleural fluid, there is progressively less expansion and elevation of the affected side. The presence of pain always still further limits thoracic motion. Diminished motion may often be apparent as a delay in expansion of the lower parts of the chest during the first part of inspiration. With large amounts of fluid, expansion and elevation may be absent. The intercostal spaces in spare individuals may be seen to have lost their normal depression and may even be widened and fuller than normal. An increase in size can be confirmed by the tape, even as much as an inch or an inch and a half greater than the opposite side. The skin may appear somewhat shiny and smooth from obliteration of normal furrows and depressions. (Edema of the skin and dilatation of the superficial veins may occur, but are rare with serous effusion. Weisz¹ finds that the phonation phenomenon (visible voice vibrations) is transmitted through fluid and may separate its lower limit from the upper border of the liver.

In consequence of the fulness of the affected side, the distance between the median line and the nipple in front and the scapula behind may exceed that on the normal side. With large effusions the corresponding hypochondrium may be fuller; the shoulder and with it the outer end of the clavicle stand at a higher level. Following partial or complete absorption or withdrawal of fluid, the affected side may be somewhat diminished in size and the intercostal spaces narrowed. Slight lateral deviation of the spine may accompany this retraction. Retraction and scoliosis are much less marked after serous than after purulent fluids.

The diaphragm shadow is absent on the side of the effusion. It usually

¹ *Prag. med. Woch.*, 1905, xxx, 261.

remains absent after recovery, but may return, although practically always of diminished amplitude. The position of the cardiac impulse should be inspected. Evidence of pleuropericardial adhesions may be obtained by systolic depression of the intercostal spaces in an abnormal position in the cardiac region.

Rarely *pulsation* of the chest wall may be observed with serofibrinous effusion, but is more common with pus. The pulsation may be confined to a locally bulging area; it may be circumscribed without tumor or may be diffuse.

Palpation.—This may confirm the results of inspection. A difference in the expansion of the two sides, the condition of the intercostal spaces, the degree of separation of the ribs, the position of the cardiac impulse and pulsations in other parts of the chest may be more evident to the hand than the eye. Pulsation, indeed, may be so slight as to be appreciated only by the hand. A narrowing of the interspaces may occur early in the disease from spasm of the intercostals, and is an important sign. The interspaces may be narrowed even when the affected side is increased in size. A friction rub may be felt before the onset of effusion; it may be palpated outside the limits of fluid during the course of the disease and may return following absorption. The temperature of the affected side is higher. Edema and fluctuation are rare with serous effusion. The liver or spleen may be displaced downward. The diaphragm may be so far depressed as to be felt below the costal margin.

The *tactile fremitus* is practically always absent; it is rarely present, but usually even then diminished, in children, with adhesions between the visceral and parietal pleura, or with small effusions. This is one of the most important signs of fluid; and the dividing line between lung and fluid can often be sharply drawn at the level at which the voice vibrations are lost. The tactile fremitus above the fluid may be diminished, maintained, or increased, depending on the condition of the pleura and the lung. Unfortunately, fremitus cannot always be obtained in women or children, owing to the high pitch of the voice, or the presence of an abundant layer of subcutaneous fat. Acute or chronic inflammatory thickening of the pleura diminishes, although it practically never abolishes, the fremitus. In the performance of thoracentesis a localized area where fremitus is maintained should not be chosen because of the possibility of pleural adhesions at this place.

Percussion.—Light is far superior to heavy percussion in bringing out slight changes. Early in the disease, when there is only a small amount of fluid, no change in the note may be detected. As the fluid increases, there is dulness at the base. As the fluid rises, the note becomes less resonant and finally flat. The regions of flatness and absent tactile fremitus correspond. The percussion note over effusions of considerable size is of short duration, lacking in volume, of high pitch, very nearly like the note obtained on percussing the thigh. It is very difficult to mark on the chest the exact upper limit of fluid. With considerable fluid, three zones with well-marked differences in the percussion note can be made out. Normal or diminished vesicular resonance may be obtained in the uppermost parts of the chest. Between this region and

the fluid the note is dull, but has a tympanitic quality (Skoda's resonance), due to retraction or compression of the lung and vibration of air in the bronchi or trachea. Below, there is flatness from fluid. The intermediate dull or dull and tympanitic area is usually most marked behind in the interscapular region, but with large effusions may be detected in front under the clavicle. If an arbitrary distinction be made between resonance and dulness and dulness and flatness, a triangular area of dulness or dull tympany can be marked out in the interscapular region, between the relatively normal lung above and the fluid below. This triangle has for its base the vertebral column, for its lower side the lower limit of lung, corresponding to the beginning of flatness, for its upper limit the beginning of dulness. The triangle represents the retracted or compressed lung, which may be apposed to the chest wall in this region. Its recognition is important for the correct determination of the upper limit of the effusion. The tympanitic note observed above the layer of fluid, as over pulmonary cavities, may change in pitch with the mouth open and closed (Williams' tracheal tone) during inspiration and expiration (Friedreich's phenomenon), and on changing the position of the patient (Gerhardt's phenomenon). A cracked-pot sound also may be heard in the absence of cavity.

With right-sided effusion, the dulness merges below with that of the liver. On the left, the tympany from inflation of the stomach with gas may be confusing and mask slight changes in the note from fluid. With considerable fluid in the left pleura, the normal tympany of the semilunar space between liver and spleen (Traube's semilunar space) may be obliterated.

Curved Line of Flatness in Pleural Effusions.—The limitation of fluid by dulness by some observers and flatness by others is responsible for much confusion in the description of the upper border of fluid. If the dull triangle mentioned above be included, the upper limit is nearly horizontal behind. With a small or medium effusion, however, the line of flatness only should be regarded as indicating its upper limit. Ellis, of Boston, correctly traced the curve, with Garland¹ verified clinically and explained by a series of experiments. It is best indicated by light percussion. With small or medium effusions, the general shape of the curve is that of an elongated "S," lowest behind, advancing upward and forward to the axillary region, where it is highest, thence to slope gradually downward. With large effusions the curve may be flattened out to assume a more nearly horizontal line. The curves of the line of flatness correspond to the line of apposition between the lower border of the lung and the pleural fluid. The curve may be of diagnostic value as a confirmatory sign of pleural effusion.

Shifting Dulness.—Dulness due to pleural effusion shifts on changing the position of the patient. This is especially true of small and recent effusions. It is absent in the presence of encapsulating adhesions and may be slight or absent with large effusions. Due allowance must be made for normal changes in the percussion note over the chest in different

¹ *Boston Medical and Surgical Journal*, September 17, 1874, and *Pneumodynamics*, Boston, 1878.

positions. The posterior inferior parts of the lung, where the test is usually made, normally become more resonant when the patient assumes a horizontal position, as in bending forward or lying face downward. The maintenance of one position during the development of an effusion is capable, to a certain extent, of modifying the location of the fluid. If the patient has been constantly on his back, the upper limit is likely to be higher behind, and small effusions may be confined to the back and the posterior axilla. It should be remembered in testing shifting dullness that the fluid may change its position only slowly.

Sense of Resistance.—In addition to the lack of resonance or other peculiarities of the percussion note appreciated by the ear, the lack of vibration and sense of resistance may be apparent to the finger as well.

Auscultation.—Early in the disease, a friction rub may be heard. Its presence does not exclude fluid, which may exist between lung and diaphragm or in the neighborhood of apposed pleural surfaces. With small effusions, the rub not infrequently persists in the lower anterior or lateral portions of the chest. The disappearance of this sign as fluid accumulates is probably due not so much to intervention of fluid between lung and chest wall as to the mechanical obstruction to the expansion of the lung. The reappearance of friction in cases with pleural effusion is favorable, indicating diminution or disappearance of fluid, provided extension of fibrinous pleuritis to previously uninvolved parts be excepted.

Crepitation, resembling that in the early stage of lobar pneumonia, and audible at the base of the lung, may also be heard in cases which later develop demonstrable fluid. Its explanation is not clear. It may be ascribed to fine pleural friction, to air entering fluid in alveoli underlying an inflamed pleura, and to expansion, during inspiration, of a slightly retracted and atelectatic lung, giving rise to crepitation coincident with the separation of previously apposed alveolar walls. A similar sound may also be heard at the termination of the disease, and may indicate that the pleural layers are again approximated, or that air is again admitted to the base of the lung.

Breath Sounds.—Changes in the breath sounds in uncomplicated pleural effusion are due to several factors, more than one of which usually operate in any given case. They depend on diminished expansion of the lung, from spasm or paralysis of the respiratory muscles, to changes in the lung itself from retraction or pressure, and to the presence in the pleural cavity of fluid which modifies or may even abolish the vibrations conducted from the lung to the chest wall.

Early in the disease irritation of the pleura and pain diminish the respiratory murmur from spasm of the respiratory muscles and fixation of the side. In the presence of fluid, the retraction and increased density of the lung may give rise not only to a diminution in the intensity of the respiration, but to a change in its character. With small effusions, the inspiration is merely diminished; expiration is abnormally long, somewhat higher pitched, and slightly bronchial in character. As the fluid increases the breathing over the base may have a distinctly tubular quality. This is often most marked in the interscapular region above the level of the fluid. With large effusions the breathing is vesicular

in the upper part of the chest; it may be bronchial above and absent below the level of the fluid. When the lung is completely retracted and compressed, there may be almost no respiratory murmur over the affected side. At times the breathing may have an amphoric character in the upper part of the chest. Rales, as well as bronchial breathing, may have a metallic quality and thus suggest cavity. In children the breathing is more likely to be bronchial than in adults. With the subsidence of the effusion the vesicular breathing returns, but may for long or even permanently remain somewhat diminished. As the atelectatic lung expands, rales can usually be heard. An accompanying catarrh or edema of the lungs may give rise to rales on the side of the effusion which may have a consonating quality. The breathing over the unaffected lung is often increased with prolongation of expiration.

Voice Sounds.—The voice sounds are often increased above, diminished or absent below the level of the fluid. The voice may have a peculiar nasal or bleating quality, the so-called *cerophony*. It is most often heard in the posterior and lower thoracic regions. The whisper is variable, but in general is increased over the region where bronchophony is heard, and may have a bronchial character. It is usually diminished or absent over the fluid. It is said by Baccelli to be transmitted through a serous and not through a purulent exudate, but the sign is not reliable.

Examination of the Heart. Dislocation of the heart is one of the most important signs. The position of the visible impulse should be noted. It may be seen to either side of the sternum. If the apex is behind the sternum, there may be no visible pulsation. At times an impulse is seen below the ensiform in the upper epigastric region. In some cases pulsation can be neither seen nor felt and reliance must be placed on auscultation. A systolic murmur is not infrequently heard over the displaced heart, and is probably due to pressure on the great vessels, especially the pulmonary artery.

Special Physical Signs.—1. *Displacement of the Heart.*—(a) *Away from the Affected Side.*—An accumulation of air, fluid, or other foreign material in one pleural sac allows the lung on that side to contract, and thus exhausts a part of its elastic force. The intrapleural tension on the affected side is correspondingly increased, while that on the unaffected side is still maintained at or nearly at its former level. The mediastinum is thus subjected on either side to unequal pressure, and seeks a position of equilibrium between the two. Because of the firmness with which the mediastinum as a whole is held in place by ligamentous bands and bloodvessels branching in various directions, its displacement is less marked than that part of it occupied by the heart, which is attached above to the relatively immobile aorta, but is elsewhere capable of considerable lateral motion within the elastic parietal pericardium. It seems more in accordance with mechanical factors to regard cardiac displacement as due to a thrust or “push” of the relatively higher intrapleural pressure in the diseased sac than a “pull” from the relatively lower pressure in the normal side.

Provided the heart is free to move laterally, its displacement may be one of the first signs of an accumulation in the pleural sac. The intra-

pleural pressure on the diseased side need not be actually positive. Apposition of fluid or other material to the heart is not a necessary factor. Because of the normal position of the heart to the left, it is always displaced a greater distance to the right with left-sided pleural disease than to the left with disease of the right pleura. The amount of fluid in the left chest may reach 700 cc. without displacement of the heart. The writer saw slight cardiac displacement develop under observation in a girl of fourteen, from whose left pleura 250 cc. of pus was evacuated. As much as 1000 cc. may be present in the right pleura without evident displacement of the heart to the left. In such diseases as pneumonia, in which pleural fluid may occur as a complication, or in cases in which its presence is suspected, a careful record of the position of the heart may be of unexpected value later in the course, when a slight deviation from its originally recorded position may be a deciding factor in a diagnosis, otherwise doubtful because of pulmonary changes complicating the physical signs. Since cardiac displacement depends not only on a loss of retractile force in the lung on the diseased side, but also on the maintenance of elastic tension in the opposite lung, any interference with the latter will limit the cardiac excursion toward that side.

(b) *Toward the Affected Side.*—Occasionally in the course of long-continued pleural disease, absorption may lead to an increase of negative pressure on the diseased side. The heart may then be pushed toward this side by the relatively greater but still negative pressure in the unaffected pleura. Thus far mention has been made only of cardiac displacements from differences of intrapleural pressure. The heart may, however, actually be pulled to one side by the contraction of adhesions between it and neighboring structures.

(c) *Position of the Displaced Heart.*—The studies of Powell, Ferber, Bard, Pitres, and others show that in the displacement to the right with left-sided effusions the heart practically always maintains its position with the apex to the left of the base, pulsation to the right of the sternum arising at the base of the heart. In Lafforgue's¹ case, however, with a large effusion of blood in the left pleural sac, the heart was found at autopsy pointing to the right.

2. *Diaphragm Phenomenon.*—This sign is of value in unilateral pulmonary or pleural disease. It is diminished in amplitude and abnormally low or absent in the presence of pleural fluid or air.

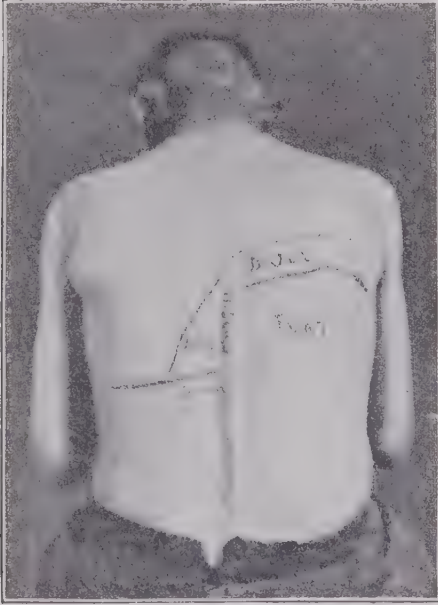
3. *Paravertebral Triangle of Dulness.*²—The presence of a normal triangle of dulness at either side of the spinal column in the inferior thoracic region makes the pathological triangle more difficult of interpretation and somewhat limits its value as a diagnostic sign. Having determined the limits of a suspected effusion by percussion and similarly outlined the lowest limit of pulmonary resonance on the unaffected side, the spinous processes of the vertebræ are percussed from

¹ *Gaz. des hôp.*, 1902.

² The triangle was first noted by Korányi in 1897 (in the fourth volume, p. 717, of *Belgógyászati Kezikönyve*, and again in Eulenberg's *Realenzyklopädie der gesamten Heilkunde*, xiii). It was independently rediscovered and more fully described by Grocco (*Riv. crit. di clin. med.*, Firenze, 1902).

above downward and the point noted where relative dullness begins. This usually corresponds to the level of relative dullness on the affected side, and somewhat higher than the level of flatness. Percussion of the unaffected lung in horizontal lines toward the spinal column discloses a paravertebral area of relative dullness of a triangular shape. The vertical

FIG. 56



Aortic insufficiency; hydrothorax on the right side; paravertebral triangle of dullness on the left. (Thayer and Fabyan.)

side of the triangle coincides with a line drawn through the spinous processes of the vertebræ, the base with the limit of pulmonary resonance on the sound side. Its outer side is formed by a line extending obliquely downward and outward. The height of the vertical and the width of the base line vary with the size of the effusion. On changing the position from the upright to the horizontal, the dull triangle nearly or quite disappears unless the fluid is encapsulated. The respiratory murmur, the voice sounds, and fremitus are diminished over this area, but the changes are less marked than on the affected side. The character of the fluid appears not to influence the triangle.

The dull triangle is practically constant in the presence of free pleural fluid or of encapsulated fluid in contact with the spinal column. In explanation of the

phenomenon, Baduel and Siciliano¹ suggest that fluid intervening between the spine and resonant lung inhibits the capacity of the former for sonorous vibrations, thus acting as a mute. The diminished resonance extends into the paravertebral region and increases in width from above downward, since the fluid at its base comes into wider contact with the spinal column and extends farther toward the opposite side. Displacement of the mediastinal contents and compression of the sound lung may play a part in its production.

Blood.—The number of red cells and the amount of hemoglobin present no striking features beyond usually not more than slight grades of secondary anemia. **White Cells:** In general, it may be said that the leukocytes in primary serofibrinous pleuritis are only rarely above normal in the absence of complications. Infectious pleuritis, on the other hand, is usually accompanied by leukocytosis. The white count, therefore, may be of value in distinguishing the two forms of the disease.

¹ *Riv. crit di clin. med. Firenze*, 1904, v, 5, 21, 37.

Tuberculous Effusion: Of 33 cases of primary serofibrinous pleuritis in which tubercle bacilli were found in the fluid, the white count was above 12,000 in only 3 (9 per cent.). In 301 primary cases, of doubtful but probable tuberculous nature, the white count was 12,000 or over in 57 (18.9 per cent.). *Infectious (non-tuberculous) Pleuritis:* The *metapneumonic* effusions are, as might be expected, accompanied by an increase of the white cells. Of 28 cases in this class the leukocytes were above 12,000 in all but 6 (78.5 per cent.). *Differential Count:* Aside from the occasional presence of eosinophilia in hemorrhagic effusions, there appears to be nothing characteristic in the differential count in serofibrinous effusion. Of 17 cases, the relative proportion of white cells showed nothing remarkable with the exception of a relative increase in the polynuclear cells in cases with leukocytosis and an eosinophilia of 20 per cent. in 1 of 5 cases with bloody fluid.

Spleen.—This is rarely, if ever, enlarged unless some complication exists. It may be palpable from dislocation with left-sided accumulation.

Axillary Glands.—Rarely the axillary glands on the affected side may be enlarged by extension of the pleural disease, whether simple, tuberculous, or malignant.

Inequality of the Pupils.—This may in rare instances occur from involvement of the sympathetic nerve. The difference is usually slight.

Blood Pressure.—This is usually normal with pleural effusions, compensation for intrathoracic pressure being maintained by increased respiration. When this compensation fails, however, there may be a fall of pressure. Capps¹ noted an increase of blood pressure during the excitement preceding thoracentesis. There was a constant fall during the withdrawal of the fluid, the average in 19 observations being 20 mm. Hg. Evacuation of large amounts of fluid, rapid withdrawal, long duration of the effusion, senile changes in the bloodvessels and heart, increased the fall of pressure.

Radioscopy.—This may confirm the results of physical examination, showing the limits of the effusion, the position of the displaced heart and the diaphragm. It may also show the presence of unsuspected pulmonary processes. It is especially valuable in locating an encapsulated effusion. The fluoroscope admits of examination from different points of view in rapid succession, but the radiograph is, in general, to be preferred. Permanent records, for study and comparison, are thus secured. The plates are more satisfactory if the patient can hold his breath during the exposure. Pleural adhesions may be suggested by a lack of diaphragmatic excursion. Thick pleura without fluid may be indicated by a lack of uniformity, by irregular limitation of the shadow and an absence of depression of the diaphragm and dislocation of the heart. The shadow is less dense than with fluid. In the presence of pleural fluid, the shadow is more uniform, more sharply outlined, and when the fluid is free occupies the lower part of the pleural space. Its upper border is curved, unless pneumothorax is present, when it assumes a hydrostatic level. A comparison of plates taken with the patient upright

¹ *Jour. Am. Med. Assn.*, 1907, *xlvi*, 22.

and lying down confirms the clinical observation of the mobility of fresh serofibrinous effusions. The shadow produced by serous is less dense than by purulent or hemorrhagic fluid.

Complications.—Lesions having an etiological relation with the disease have already been considered. It is difficult oftentimes during life or even at the postmortem table to separate them from conditions dependent on the pleuritis. These secondary processes only need be considered here. Tuberculosis may rarely extend from pleura to uninvaded lung. The progress is usually, however, from lung to pleura. Acute miliary tuberculosis may rarely complicate or follow serofibrinous effusion. Infection may extend to the opposite pleura, the pericardium, peritoneum, or other parts of the body. Perihepatitis or perisplenitis may thus arise. Thrombosis of the pulmonary vessels, the venæ cavæ, heart, iliac, femoral, saphenous, or other veins may be associated with increased intrathoracic pressure and infection. Embolism may be rapidly fatal. (Edema of the lungs is a constant danger in large accumulations and with untapped effusions is probably due to cardiac insufficiency. Perforation of the lung or thoracic wall complicates purulent effusions with unfortunate frequency, but is rare with the serofibrinous form. It has been noted by Sahli¹ and Sokolowski. Nephritis probably bears only a chance relation to pleuritis. It arose under observation in only 1 of 500 cases in the writer's series.

Causes of Sudden Death.—Death may be due to associated and independent lesions to which the pleuritis is secondary. Such causes need not be considered here. Of causes dependent on the serofibrinous effusion, thrombosis and embolism are among the most frequent. The pulmonary vessels, the auricles, the venæ cavæ, iliac and femoral veins often contain thrombi, which may give rise to emboli, with rapidly fatal pulmonary embolism, as in 5 of 14 autopsies in the writer's series. Cerebral embolism is less common. (Edema of the lungs may be the only associated lesion found, as in one case with a double effusion. Post-mortem examination does not always disclose the immediate cause of death, which has then been thought to be due to compression of the aorta (Trousseau), or to a kink or twist in the inferior vena cava (Bartels), but Osler in a number of observations was unable to substantiate the latter. Cerebral anemia, from a mechanical hindrance to the circulation, is a possible cause. Pressure on the venæ cavæ, and the heart itself, especially the auricles, may embarrass the cardiac mechanism, resulting not only in cyanosis, rapid, feeble pulse, and dyspnoea, but even syncope and death. Various factors may operate in individual cases. Large double or left-sided effusions are more dangerous. Death may follow sudden change of position, an attack of pain, deep respiration, or a paroxysm of cough.

Duration.—In the writer's series of 369 cases of primary serofibrinous pleuritis, the time from the beginning of symptoms to discharge from the hospital was less than three weeks in 53, three to six weeks in 167, six to nine weeks in 60, nine to twelve weeks in 43, three to six months

¹ *Mitth. aus klin. und med. Inst. der Schweiz.*, 1894.

in 31, six months to one year in 12, two years or over in 3. Thus, about 60 per cent. ran their course within six weeks, about 87 per cent. within three months. The duration is longer with large effusions, in old and debilitated patients, in the presence of complications, in untapped cases or those in which evacuation is delayed. It is shortest in primary effusions, in young and otherwise apparently healthy individuals, treated by early tapping.

Relapse.—Although it is not uncommon after withdrawal of fluid for for it to reaccumulate under observation and necessitate one or more tappings, it is rare for a serofibrinous effusion to reappear on the same side after it has been fully absorbed or removed. The obliteration of the pleural sac following serofibrinous effusion is probably responsible for the rarity of true relapse.

Sequelæ.—It is rare for serofibrinous effusions to change from serous to purulent. Of 1185 cases, empyema developed in only 16 (1.3 per cent.). When empyema follows serofibrinous effusion, the fluid has usually been turbid, with an excess of polynuclear cells from the beginning. Spontaneous or artificial pneumothorax may occur, and, if the communication is through the lung, infection may follow. Imperfect technique in tapping may cause empyema. Slight dulness, diminished expansion, breathing, and fremitus last for a variable period after the disappearance of serofibrinous fluid. The intercostal spaces may be slightly narrowed and the affected side somewhat smaller. These changes may be permanent, but are less common and less marked than after empyema. The heart usually returns to its normal position. Rarely it may be fixed by adhesions in an abnormal position toward the sound side or slightly displaced toward the affected pleura. Slight lateral deviation of the spine may accompany these changes.

Diagnosis.—This is usually easily made from the onset with pain, the diminution or disappearance of which is accompanied by increasing dyspnoea, the diminished expansion of the affected side, initial narrowing, with later enlargement of the side and widened interspaces, the character and distribution of the dulness, diminished or absent breathing and fremitus, and the displacement of neighboring organs.

DISEASES WITH WHICH AN EFFUSION MAY BE CONFUSED.—1. *Intra-thoracic.*—(a) *Thick Pleura.*—Following the partial or complete absorption or removal of pleural fluid, the thickened pleura may give rise to some confusion. There may be slight dulness, diminished breathing and fremitus. The side is not flat, however, the breathing only slightly altered, without bronchial character, and the fremitus, although it may be diminished, is not absent. The paravertebral triangle of dulness opposite the affected side is absent and the heart is not displaced.

(b) *Pneumonia.*—Typical lobar pneumonia is easily differentiated by its more severe onset, with chill and rapid rise of temperature, cough with rusty sputum, dulness (not flatness), bronchial breathing, increased voice, whisper and tactile fremitus, and consonating rales. The signs are often confined to parts or the whole of one or more lobes. Atypical pneumonia may closely simulate effusion. Cough and expectoration may be absent. Partial or complete involvement of the lower lobes

with occlusion of the bronchi by secretion (massive pneumonia) may give rise to signs of effusion. If the bronchi can be emptied by cough, the signs may then become clear. The absence of cardiac displacement is important. A narrow strip of relative resonance in the paravertebral region on the affected side with croupous pneumonia and dulness in this region with pleural effusion is of some value in differentiating the two conditions. Small amounts of pleural fluid often complicate pneumonia. Small effusions are more often serofibrinous, large amounts more commonly purulent. In doubtful cases exploratory puncture should not be delayed. Chronic suppurative changes in the lungs, with multiple bronchiectatic cavities, interstitial pneumonia and thick pleura, may closely resemble pleural effusion. The vocal fremitus may be diminished; in rare instances it may be absent, if the dilated bronchi are filled with secretion. Evacuation may be followed by a return of fremitus. The dulness is often greater in some places than in others, and is not as marked as with fluid. The side may be contracted, the interspaces somewhat narrowed, and the heart in normal position or slightly displaced toward the affected side. The diaphragm may be elevated, the diaphragm phenomenon diminished in amplitude or absent. Exploratory puncture is attended with some danger of perforating the elevated diaphragm, of bleeding from injured bloodvessels or granulation tissue, or the infection of an intact pleura in the withdrawal of the trocar. If pus is found, it may come from pulmonary cavities.

(c) *Tumors of the Lung and Pleura.*—Tumors which reach the periphery of the lung may give rise to some confusion. There may be flatness, diminished or absent breathing, and fremitus. The site and contour of the process may differ from pleural fluid. Bloody sputum, dyspnoea, stridor, paralysis of the vocal cords, dysphagia, dilatation of the cervical or thoracic veins and superficial metastases may be suggestive. If the pleura is invaded by the new growth, an effusion is common and this may mask the pulmonary process. Exploratory puncture may evacuate bloody fluid. Echinococcus of the lung or pleura may simulate serofibrinous pleuritis.

2. *Abdominal Affections.*—Subdiaphragmatic abscesses and tumors, especially echinococcus cysts, may simulate an accumulation of pleural fluid. Abdominal pain, tenderness, and muscular spasm may be due to diaphragmatic pleurisy.

DETERMINATION OF THE CHARACTER OF PLEURAL FLUIDS.—This is impossible in most instances without exploratory puncture, but certain suggestive features may be mentioned. Hydrothorax is most easily distinguished from the presence of cardiac or renal disease or both, bilateral fluid, which shifts more readily on changing the position of the patient, and œdema elsewhere, as well as absence of pain, fever, leukocytosis, and friction rub. In unilateral hydrothorax without general dropsy the distinction may be impossible. Hemorrhagic fluid may be suspected following trauma, when the effusion is secondary to malignant disease, or with an eosinophilia in the circulating blood. Chylothorax can hardly be distinguished, but may be suspected with the known presence of chylous ascites. Empyema, in typical cases, may be differ-

entiated. It is more likely to be secondary and metapneumonic, while serofibrinous effusion is much more likely to be primary. If the patient is a child and under five years, the chances are much in favor of pus. The symptoms are of little assistance in individual cases, but in general are more severe in empyema, with higher and more irregular fever, chills, sweats, and more rapid loss of flesh, strength and color. Edema of the skin, dilatation of the superficial veins, thoracic pulsation, perforation of the lung or other organs may suggest empyema. A leukocytosis above 12,000, unexplained by other features, suggests an infectious process and usually means pus.

Exploratory Puncture.—This may be done without pain as follows: The site of the puncture is frozen with ethyl chloride spray. The syringe is filled with about 2 cc. of sterile water containing $\frac{1}{3}$ gr. novocaine and $\frac{1}{200}$ gr. adrenalin and the needle introduced through the frozen area. The needle is thrust inward by degrees, perpendicular to the surface, each advance being preceded by the injection of a small amount of the fluid into the tissue in front of the point. The rib is passed close to its upper margin to avoid the intercostal artery and after the pleural sac is reached the syringe should still contain some fluid which may be used to dislodge from the lumen of the needle any fibrin or other material preventing aspiration. Thick pus may fail to flow through a small needle. In addition to the determination of fluid, the operator may appreciate any unusual thickness or density of the pleural or pulmonary tissue by the amount of resistance encountered by the instrument (palpatory puncture). In rare instances a diagnosis between pleural and subdiaphragmatic fluid may be made. By the removal of the syringe and the attachment of a rubber tube to the needle, the apparatus is converted into a siphon and the amount of pleural pressure may be determined, as suggested by Krönig. The normal depression during inspiration and elevation during expiration of the column of fluid may be reversed in subdiaphragmatic collections. The withdrawal of small amounts of fluid by exploratory puncture is occasionally followed by rapid spontaneous absorption of what remains.

In rare instances, if the needle is used for exploratory puncture, the microscopic examination of a piece of tissue caught in the lumen may furnish the diagnosis. In one of the writer's series a tubercle was thus demonstrated. Prentiss¹ made the diagnosis of sarcoma and Steele and Girvin² of carcinoma of the pleura by this means.

EXAMINATION OF PLEURAL FLUIDS.—Under normal conditions there is merely enough pleural fluid to lubricate the apposing surfaces, and as yet no chemical analysis of this has been made.

1. *Chemistry.*—Pleural fluid may be *serous*; it may contain varying amounts of fibrin, when it is known as *serofibrinous*; it may also vary in its content of blood and pus and may then be termed *hemorrhagic*, *fibrinopurulent*, or *purulent*. The presence of chyle justifies the term *chylous*; of fat not due to chyle, *chyliform*.

¹ *Transactions of the Association of American Physicians*, 1893.

² *Proceedings of the Pathological Society of Philadelphia*, 1901.

Transudates and Exudates.—It is customary to make a clinical distinction between fluids resulting from hydremia and stasis or transudates and those arising in the course of inflammatory processes or exudates.

In general, transudates are of relatively low specific gravity and contain a small amount of albumin, *i. e.*, a specific gravity of 1010 or under for hydremic fluids, with traces to 1 per cent. of albumin; and 1010 to 1015 in venous transudates, with 1 to 3 per cent. of albumin. Only a very slight precipitate follows the addition of a few drops of acetic acid to the fluid. It coagulates slowly or not at all, unless mixed with blood. The specific gravity of exudates, on the other hand, is usually 1018 or higher, with 4 per cent. or more of albumin. They show a more abundant precipitate on the addition of acetic acid (see page 1014), contain a larger amount of fibrinogen, and usually coagulate rapidly with or without the presence of blood. For the estimation of albumin Esbach's test may be used, but is only approximately accurate, and for more exact determination more complicated methods must be employed, such as the weight of the precipitated proteid or the total nitrogen (Kjeldahl).

2. *CYTOLOGY.—Cytodiagnosis.—Technique.*—The fluid should be examined as soon as possible after withdrawal. To prevent spontaneous coagulation and the entanglement of cells in the meshes of fibrin, it may be placed at once in a sterile flask containing about one-third to one-half its volume of 1 per cent. sodium citrate in 0.85 per cent. salt solution. The sediment is obtained by centrifugalization, the supernatant fluid carefully decanted, and thin smears made with the platinum loop. These are allowed to dry in the air or over the Bunsen flame. Care must be taken not to burn the preparation. Wright's blood stain is allowed to remain on the cover-glass from one-half to one minute, then diluted with 8 to 10 drops of water, and allowed to stand one to two minutes. The preparation is washed in a gentle stream of tap water, dried over the Bunsen flame, and mounted in balsam.

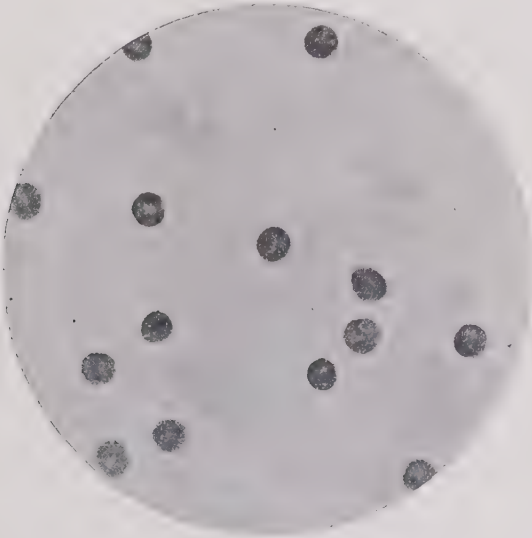
Red cells are of relatively little importance in the microscopic examination. A differential count should be made of the white cells. Polynuclear neutrophiles correspond to similar cells found in the circulating blood. Eosinophiles are often found in small numbers, mast cells less often. The lymphocytes correspond to similar cells in the blood. Endothelial cells are large, flat, irregular, round, or oval in contour with a round or oval blue nucleus, which is poor in chromatin and often vacuolated. They may be isolated or in plaques, the so-called "*Placards endothéliaux*." Unfortunately, between typical examples of lymphocytes and endothelial cells there are atypical forms of mononuclear leukocytes which cannot be fairly classed with either of the two groups. Such atypical cells, however, usually comprise but a small proportion of the white cells, and may thus introduce a negligible error in the differential counts. In some cases, the classification of the cellular elements is impossible because of degenerative changes.

Cytological Formula.—Widal¹ stated that (1) a predominance of polynuclear leukocytes means an effusion of infectious origin (pneumococcus,

¹ Widal and Ravaut, *Compt.-rend. de la Soc. de biol.*, 1900, p. 648

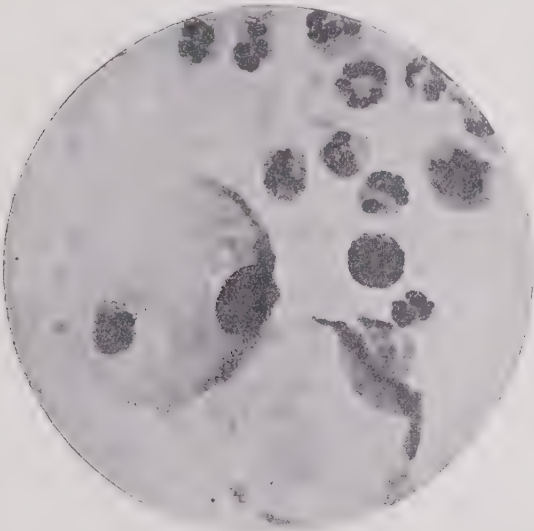
streptococcus, staphylococcus); (2) of lymphocytes, a tuberculous effusion; and (3) of endothelial cells, especially if in plaques or sheets, an effusion of mechanical origin. Recent observations make it probable that the

FIG. 57



Lymphocytosis. Case of primary tuberculous pleurisy. $\times 750$. (Musgrave.)

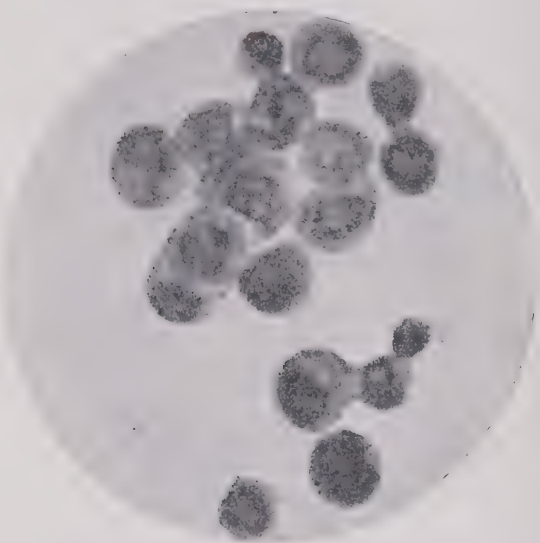
FIG. 58



Large phagocytic endothelial cells and polynuclear leukocytes. Case of acute infectious pleurisy. $\times 750$. (Musgrave.)

character of the cells in pleural fluids depends not only on the cause of the process, but also on the intensity of the pleural reaction. The predominance of one type of cell, therefore, cannot be regarded as a specific indication of an infectious, tuberculous, or mechanical origin. An excess of polynuclear leukocytes in infectious pleuritis is subject to least variation. A transient excess of polynuclear neutrophils has been found in early pleural tuberculosis. The secondary infection of a pleura already the site of tuberculosis may modify the character of the cellular elements, with an increase in the relative proportion of polynuclear cells. In mechanical effusions, endothelial cells are relatively most numerous in the early stages. In long-standing transudates, lymphocytosis may be present without a reaction to tuberculin and in transudates shown by

FIG. 59



Endothelial plaques and cells. Case of hydrothorax due to cardiac disease.
× 750. (Musgrave.)

autopsy not to be tuberculous. As in fluids with lymphocytosis, so, also, in those with an excess of endothelial cells, an infection may raise the number of polynuclear cells. In malignant disease of the pleura, the cellular elements conform more nearly to those found in mechanical effusions, with an excess of endothelial cells, but large numbers of spindle cells may suggest sarcoma, as in Warthin's case. The value of cytology in the diagnosis of pleural effusions has proved somewhat less than was at first anticipated. The exceptions are too numerous to admit of definite conclusions from the cells alone, but the method is of assistance with other factors in any given case.

3. *Bacteriology.*—For the demonstration of the pneumococcus, the pyogenic cocci, and other organisms capable of cultivation, smear preparations should be made and suitable media inoculated.

Tubercle Bacillus.—Special methods are used for its demonstration.

Inoscopy.—Jousset,¹ in 1903, proposed a simple method for the demonstration of tubercle bacilli in coagulable fluids. After withdrawal, the fluid, at least 100 cc. in amount, is allowed to clot. The clot is removed and washed free of serum on sterile gauze, with sterile water, then placed in a flask containing 10 to 30 cc. of the following digesting fluid: pepsin, 1 to 2 grams, pure glycerin and strong hydrochloric acid of each 10 cc., sodium fluoride 3 grams, and distilled water to 1000 cc. The flask is placed in the incubator at 38° C. until the clot is digested. Two to three hours are usually needed. Frequent agitation of the fluid hastens the process. The digested fluid is sedimented, the supernatant fluid decanted, and from the precipitated material smears are made with the platinum loop. These are dried and stained for tubercle bacilli.

Sedimentation.—Zebrowski² takes at least 100 cc. of fluid, adds an equal volume of 1 per cent. sodium fluoride to prevent coagulation, and allows the solution to stand in a cool place for twenty-four hours. The supernatant fluid is decanted and the precipitate centrifugalized. Smears made from the material thus obtained are investigated for tubercle bacilli, as already described. The greatest care should be taken that bacilli in fluids previously examined are not left clinging to the apparatus.

Animal Inoculation.—Intraperitoneal inoculation of guinea-pigs is most successful. For the demonstration of tubercle bacilli, large amounts of fluid must be injected, but in divided doses. If the animal lives, three months should be allowed to elapse before the examination is made. Le Damany³ made injections each week of 10 to 50 cc. of fluid, varying the amount according to the toxicity of the fluid, and was thus able to inoculate as much as 300 cc.

Prognosis.—In general, the immediate prospect in serofibrinous pleuritis is good. Large or double effusions may, however, be suddenly fatal. Of 500 cases in the writer's series, 4 (0.8 per cent.) died without other obvious cause than the effusion. In one, large amounts of fluid rapidly reaccumulated, conforming to the uncommon variety known as pleuritis acutissima. No autopsy was obtained. The three remaining patients were not tapped. Two had double effusions, in one of whom autopsy showed that death was due to pulmonary embolism; in the second no other cause of death was found postmortem than œdema of the lungs. In the last patient there was a large unilateral accumulation, and examination after death showed pulmonary embolism. If an infectious and non-tuberculous cause can be established, the prognosis is favorable.

Treatment.—1. *The Natural or Spontaneous Cure*.—The large proportion of cases coming to autopsy with pleural adhesions, associated with fibrocascous or calcified pulmonary lesions, shows that pleural disease, directly or indirectly dependent on the tubercle bacillus, is frequently arrested or healed. Tuberculous nodules in the pleura, as elsewhere, may be walled off by a dense envelope of fibrous tissue, and thus prove of little danger to the individual, forming latent foci. Cal-

¹ *La semaine méd.*, 1903, p. 22.

² *Deut. med. Woch.*, 1905, No. 36.

³ *La presse médicale*, November 24, 1897, p. 329.

cification may take place, as in 5 of 27 cases (M. G. H.), with obsolete tuberculosis as a result. Tuberculous granulations in a part or the whole of the pleura may finally be converted into firm, fibrous tissue, ending in obliteration of the pleural sac and no further trouble from the process. The clinical history of cases of certain or probable pleural tuberculosis shows that recovery is not infrequent.

2. *General Measures.*—For purposes of treatment, it is best to assume every case to be tuberculous, unless there is good reason to believe otherwise. Fortunately, many patients are still in fair health when they first come under observation. The course of the disease is often slow, and spontaneous recovery too often fosters half-way measures in its care. As in tuberculosis elsewhere, we must rely chiefly on rest, fresh air, and the improvement of nutrition. It must be constantly in mind that the pleural disease is usually secondary to tuberculosis of the lung or thoracic glands.

If we are to secure the hearty coöperation of the patient, he should be frankly told the seriousness of his condition. We can otherwise hardly secure his acceptance of the necessary restrictions on his mode of life. The chances with primary serofibrinous effusion are about 3 or 4 in 10 that a pulmonary or other tuberculosis will appear within a period of six or seven years. These figures have this hopeful aspect, however, that they are for the most part gathered from cases in which treatment terminated with the disappearance of the effusion. They probably, therefore, represent the natural evolution of the disease, and a longer or even a permanent arrest may be expected in patients who can and will consent to more careful supervision and regulation.

During the acute stage, while there is fever, *rest* in bed should be enforced and maintained until the temperature is normal. After the acute symptoms have subsided, the patient may cautiously be given greater liberty, careful watch being kept meanwhile on the temperature. The supply of fresh air should be continuous and abundant, by night as well as by day. Means similar to those in pulmonary tuberculosis may be taken to secure this. In undernourished individuals an increase in weight should be sought from the beginning, and for such patients extra feeding must be employed. The food should be simple and nutritious and extra feedings of milk or eggs may be given between the regular meals. Fat is important and is best given as cream or fresh butter.

The treatment should not end with the subsidence of fever and the disappearance of fluid. Patients who have apparently recovered should be kept under observation, and every effort made to maintain the general condition at a high level. Country is better than city life and the occupation should be carefully chosen. Overcrowded, dusty, or badly ventilated places should be avoided. Indiscretion and neglect may bring the patient under observation a second time with pulmonary or other tuberculosis too late for successful treatment. Loss of weight, fever, cough, or other symptoms should receive attention, and if necessary, a further course of rest, outdoor life, and extra feeding.

3. *Local Applications.*—These are for the alleviation of symptoms. The ice-bag, hot-water bottle, and hot applications repeated every two

hours may efficiently relieve pain, for which, however, morphia may be necessary. It is doubtful if blisters have other than a harmful effect, making the patient uncomfortable and adding to the danger of thoracentesis, if the skin becomes infected. Strapping the affected side only further displaces the lung and other organs. It may actually hinder absorption by compressing the lymph channels.

4. *Special Measures. —Thoracentesis. —Indications.*— In general, the opinion of the present time is in favor of tapping serofibrinous effusions (1) with pressure symptoms, such as severe dyspnoea, cyanosis, or rapidly developing cardiac weakness; (2) of large amount, with dislocation of heart and mediastinum, even without pressure symptoms, and (3) of medium amount when other means have failed to bring about absorption and two or three weeks have elapsed.

With *pressure symptoms and large effusions, thoracentesis is imperative* and should be done without delay. It has been the unfortunate experience of many physicians to decide on evacuation of such cases within a given time before the expiration of which the patient has suddenly died. The presence of fever is not a contra-indication. Left-sided effusions are somewhat more dangerous. Bilateral fluid, of only medium amount, should likewise be immediately evacuated. The removal of medium and small effusions is not immediately necessary and a short delay may promote repair or furnish evidence of spontaneous absorption. It is customary to wait two to three weeks, but earlier removal may well be considered. It alleviates symptoms from pressure and may prevent the formation of venous thrombi and the danger of pulmonary infarction. The withdrawal of fibrinous material, hindering absorption, may shorten the course of the disease. The danger of adhesions, permanent fixation of the lung in an abnormal position and persistent reaccumulation of fluid increases with the duration of the effusion.

Selection of Cases for Tapping.—With clear fluid, thoracentesis is the operation of choice. With turbid fluids the decision is more difficult. They are on the borderline between serofibrinous and purulent effusions. The tendency of pleural fluid to sediment within the chest must be remembered. A sample from the upper layer may be turbid, while pus may exist below. With merely an excess of polynuclear cells in the differential count, tapping alone may be considered. Pneumococci may be found in such exudates, but are often incapable of cultivation. With abundant or necrotic leukocytes and pneumococci on cultivation, operation is usually necessary. Streptococcus infections are usually purulent, or rapidly become so, and generally demand open incision. The general symptoms, the amount of fluid and rapidity of reaccumulation must also be considered.

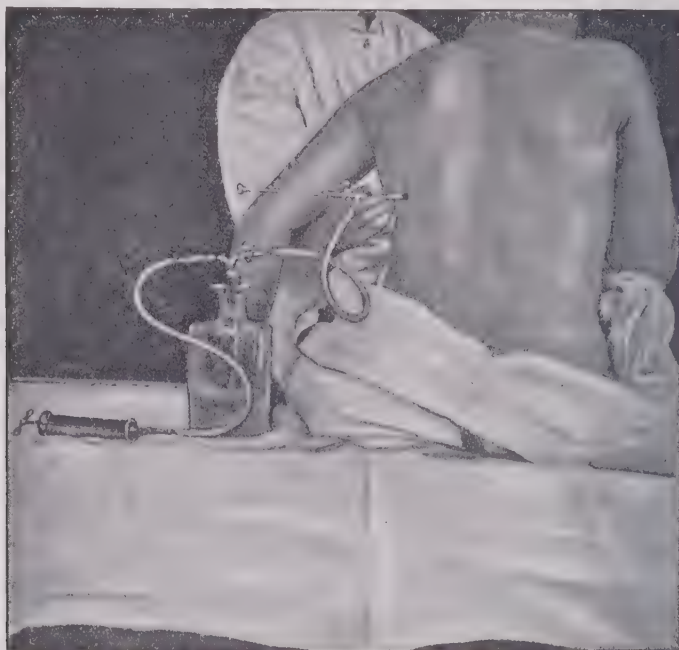
Apparatus. — Needle or Trocar?—The *needle* has two drawbacks. Its unprotected point may wound the expanding lung or the diaphragm. More important than this, however, a bit of tissue punched out during insertion or a small mass of fibrin may effectually occlude its lumen. To dislodge such particles, the needle must be withdrawn, if the danger of pneumothorax and possible infection of the pleura are to be avoided. The air-tight trocar, after the withdrawal of the stylet, presents a blunt

pointed cannula which is less likely to injure the inflamed pleura and an obstruction may be readily removed by the reintroduction of the stylet and with the instrument still in place

Various *trocars* have been devised. The writer uses an air-tight trocar,¹ with stop-cock on lateral outlet and cannula.

Aspiration.—Potain's apparatus is in most general use. The pump is capable of a dangerous degree of aspiratory force. Only sufficient aspiration should be used to just maintain the flow. The rubber tubing should be thick and all connections must be air-tight. A piece of glass tubing inserted between the trocar and bottle will be of assistance in noting the result of aspiration. If desired, a mercury manometer may readily be connected with the bottle, thus measuring the negative force.

FIG. 60



Aspiration with Potain's apparatus. (After Hoppe-Seyler.)

An extension of the inlet to the bottom of the bottle will prevent any back flow of air, provided the negative pressure within the thorax becomes greater than within the bottle. As a receptacle for the fluid a bottle of the proper size to fit the rubber stopper, graduated at different levels and capable of holding from 1500 to 2000 cc., should be chosen. The glass should be of such a quality as to stand sterilization without breaking.

Technique.—Asepsis should be carried out as carefully as for a major surgical operation. The apparatus should be set up, tested by the aspiration of sterile water, and the air in the bottle should be under negative pressure before the puncture is made. The site chosen for

¹ Air-tight trocar for thoracentesis, *Jour. Amer. Med. Assoc.*, 1908, L, 122.

puncture will vary with the amount and position of the effusion. The position of the heart must be known. An encapsulated exudate must be sought with due regard to anatomical landmarks. With large or medium and free effusions, the puncture is usually made in the seventh space between the scapular and posterior axillary lines. As the dome of the diaphragm rises normally as high as the fourth interspace in the nipple line, the sixth rib in the midaxilla and the eighth rib in the scapular line, a lower level cannot safely be chosen. In chronic cases, with narrowing of the interspaces, contraction of the side and elevation of the diaphragm, a higher level should be selected. The interspaces should be counted before the operation is undertaken. A thickness of 2 to 4 cm. or more under ordinary conditions must be allowed for the thoracic wall. In fat subjects, or in the presence of a thick layer of fibrin, the trocar may fail to find fluid even at this distance. The patient is best placed on the bed to avoid unnecessary exertion after the operation. The puncture may be made with the patient in the sitting position or reclining on the unaffected side. The intercostal spaces are widened by placing the hand of the affected side on the opposite shoulder. *Local anesthesia* as for exploratory puncture should precede the operation. The subcutaneous injection of morphia has been advised, but may inhibit symptoms which would otherwise warn the operator of approaching danger. The instrument is slowly and carefully introduced, perpendicular to the surface, just above the rib, to avoid the intercostal artery. It is pushed in until from the lack of further resistance the operator may judge that the point has reached fluid. After withdrawal pleural fluid may continue to flow from the wound. Slight bleeding from the injury of small bloodvessels may occur. Pressure usually suffices to stop this, but if necessary, a stitch may be taken through the wound. A *dressing* may be made from a small pad of sterile gauze cut to an appropriate size and held in place by adhesive plaster.

Symptoms and Difficulties during Evacuation.—Faintness and vertigo are not uncommon, and are usually due to psychic disturbance. They may be relieved by placing the patient in the reclining position and giving an alcoholic drink. An occasional slight cough is frequent toward the end of the evacuation. If severe, the operation should be stopped. Cough may be due to pleural irritation, to hyperemia, or œdema of the expanding lung. If it persists, morphine may be given. Blood may rarely be expectorated during evacuation. It may arise from the rupture of small bloodvessels in the lung, from congestion, or from puncture of the lung with the trocar, and when it occurs it is best to discontinue the operation. Pain is not common, but if severe, is a contraindication to continuance, as it may indicate undue tension on pleural adhesions. There may be a feeling of dyspnœa and general discomfort, perhaps cardiac in origin, and severe enough to warrant a halt in the operation. After introduction and the withdrawal of the stylet, no fluid may follow. A bit of fibrin may have closed the opening, or if, after reintroduction of the stylet, the puncture is still negative, the trocar may need to be inserted farther, in a different direction, or partially withdrawn. Introduction elsewhere may be more successful. Finally, there may be no

fluid, but negative punctures never positively exclude it. Interruption of the flow during evacuation may be due to fibrin, apposition of lung or diaphragm against the end of the cannula, or equalization of pressure within and outside the chest. The last may happen even with considerable fluid remaining, provided the lung is firmly bound down in a retracted position.

Amount of Fluid to be Withdrawn.—This depends on the size of the effusion. Absorption may follow removal of very small quantities. The rare occurrence of serious symptoms, and even of death, following the evacuation of large amounts of fluid is a warning not to be safely disregarded. With large effusions, as much as 1500 cc. may be withdrawn, provided no unfavorable symptoms arise during the process. Much larger quantities are often removed without an unfavorable result, and with very large effusions, in which the fluid runs without aspiration or symptoms, as much as 2000 cc. may be evacuated. If danger is to be avoided, however, this amount should only rarely be reached and never exceeded. The remaining fluid will probably be absorbed; if not, the procedure can be repeated. The longer the effusion has lasted and the older the patient, the smaller the amount of fluid which can be safely withdrawn. More abundant adhesions and less elastic lung then increase the danger. In the presence of pulmonary tuberculosis, especial care should be exercised to avoid rupture of adhesions and pneumothorax.

Duration of the Operation.—It is safer to evacuate fluid slowly. A half-hour may be consumed in the removal of 1500 cc. in order that neighboring structures may gradually readjust themselves.

Repetition of Tapping.—One tapping suffices in about 75 per cent. of the cases. In about 20 per cent. of the remaining cases there is no more fluid after the second operation. In some cases evacuation must be frequently repeated.

Dangers of Thoracentesis. There is some danger in thoracentesis. This is reduced to a minimum by the strictest asepsis, the use of an air-tight trocar rather than an ordinary needle, the slow withdrawal of only moderate amounts of fluid without forcible aspiration, and a careful selection of cases. Unavoidable accidents are extremely rare. Patients are more often sacrificed by hesitation and delay.

If performed with an imperfect technique, a serous may be converted into a purulent effusion. Of 553 tapplings in the writer's series, turbid fluids were found in 27, and of these 12 later became purulent, but the suppuration was probably spontaneous. In one instance a fluid showed 88 per cent. of lymphocytes at the first tapping and 78 per cent. polynuclear cells when the thoracentesis was repeated four days later. In a second case a fluid at first contained 96 per cent. lymphocytes. The patient was discharged without evidence of effusion, to return one month later with empyema. Whether a similar change would have taken place without puncture is uncertain.

Pneumothorax is a more frequent result. In rare instances it may be due to puncture of the lung or to the rupture of adhesions, pulmonary cavities, or emphysematous blebs during expansion. It is not infrequently due to the entrance of air through an unguarded needle or trocar.

It may also result from accidental inflation of the pleural sac with the aspirating pump, if the tubing is misapplied. Infection of the pleura may follow the admission of air.

Subcutaneous emphysema may occur if the lung is wounded and air enters the track of the trocar. It may be local or involve the greater part of the body, and is more common after exploratory puncture. Extension of malignant growth or tubercle along the track of the needle occasionally occurs. The removal of pleural fluid may lead to the detachment of thrombi in the heart or intrathoracic vessels, with monoplegia or hemiplegia as a result. Delirium and hysterical and epileptic attacks have been observed. Urticaria has been noted after thoracentesis, and should always suggest echinococcus disease.

Albuminous expectoration is of rare occurrence. Osler observed the condition twice in 195 cases. It occurred once in the writer's series. The albuminous expectoration usually begins during or shortly after the withdrawal of fluid. Its appearance may, however, be delayed for as long as eighteen hours, as in Pepper's case. It is accompanied by cough and often by dyspnoea, which varies much in intensity and may be extreme, with cyanosis and rapid, feeble pulse. Rales may be heard over the lung during the attack. Its duration and intensity are very variable. It may last for as long as forty-eight hours, and the patient may die of suffocation. The fluid may amount to as much as a quart in two hours, but smaller quantities are more common. The expectorated fluid is serous and contains a variable amount of blood, frothy mucus, and albumin. In most instances an excessive amount of fluid (more than 2000 cc.) has been removed. The condition has been ascribed to evacuation of pleural fluid by way of the bronchi. This may happen if the lung has been perforated during the puncture. Spontaneous rupture or filtration through the lung has been suggested. It is more probably due, however, to pulmonary congestion, with œdema, for which Riesman suggests the term "congestion by recoil." It may be conjectured that compression of the lung is followed by changes in its bloodvessels, and that in the congestion after re-expansion there is a transudation of serum. Of 51 cases of albuminous expectoration reviewed by the writer,¹ 13 were fatal. A consideration of the postmortem reports on 14 in whom death immediately followed the operation or occurred after an interval suggests that pulmonary inelasticity from pleural adhesions or complicating cardiac, pulmonary or mediastinal disease is probably an important contributing factor.

Death, in rare instances, has followed exploratory puncture.

Capps and Lewis² have shown that mechanical irritation of an inflamed pleura, experimentally produced in animals, frequently gives rise to a reflex of a vasomotor type which lowers the blood-pressure and may cause death. The most efficient remedy for this form of shock is the intravenous injection of adrenalin. Artificial pneumothorax has occasionally been fatal. Sudden death during or after the evacuation of pleural fluid may be due to embolism. Thrombi in the pulmonary veins

¹ *Boston Medical and Surgical Journal*, April 15, 1909.

² *Tr. Assoc. Am. Phys.*, 1907, xxii, 635.

or the venæ cavæ are the most frequent source. Syncope and death may occasionally be due to cerebral anemia, from afflux of blood to the re-expanded lung. Fatal hemoptysis has followed the wounding of vascular granulation tissue in the lung or of bloodvessels lining the walls or traversing the lumen of pulmonary cavities. Such vessels may be also ruptured during expansion of the lung. Perforation of the diaphragm has been followed by fatal peritonitis or hemorrhage from the spleen. Miliary tuberculosis may, in rare instances, arise from infected thrombi set free from pulmonary vessels by the evacuation of tuberculous fluid (Fränkel). If the lung is adherent, fatal hemorrhage from pleural vessels may follow forcible aspiration. Injury of an atheromatous intercostal artery has been followed by fatal bleeding (Naunyn).

Results of Thoracentesis.—Following removal of fluid, there is usually a marked improvement in the breathing and cardiac action. The color is better and there may be an increase in the amount of urine. The heart returns to its normal position unless prevented by adhesions or marked indurative processes. The temperature may fall at once, but gradual defervescence is more frequent. The duration and intensity of the pleuritis appear to be lessened. Re-expansion of the lung is more rapid, absorption of the remaining fluid takes place, and subsequent deformity with contraction of the side, narrowing of the intercostal spaces, and displacement of diaphragm and heart are less frequent. It is a mistake to regard such patients as cured, however, for too often the subsequent history shows that the pleural symptoms have been relieved, but that an underlying tuberculous process continues to extend.

After-treatment.—If the patient has been in the reclining position, following the operation, a bed-rest may first be given, then a change from the bed to a chair, and the patient may be up and about by the end of the week, provided no contraindications are present. This interval of quiet is wise even if all goes well, to allow time for readjustment to the changed intrathoracic conditions and repair in the pleura.

In view of their doubtful value and the importance of maintaining the general health at a high level, such measures as catharsis, diaphoresis, diuresis, and the thirst cure cannot be recommended. A reduction in the amount of sodium chloride ingested may be considered, but as yet has not been demonstrated to be of great value in the removal of inflammatory fluids. No drugs have been shown to have a specific action on pleurisy. Respiratory exercises are likely to do more harm than good with tuberculous effusions. Tuberculin may be of service, but hygienic and dietetic treatment are more important. Thoracotomy should be considered as a life-saving measure in the rare cases in which there is a rapid accumulation of serofibrinous fluid (pleuritis acutissima) too gelatinous in consistency from the presence of abundant fibrin to be evacuated by the trocar.

Acute Purulent Pleuritis.—**Etiology.**—Certain differences between the etiology of this and other forms of pleuritis may be mentioned.

Primary Form.—The proportion of cases in which empyema is apparently primary is relatively small compared with fibrinous and serofibrinous pleuritis. Of 252 cases with empyema in the writer's series, 83

(32.9 per cent.) may be classed in this group against 64 and 63 per cent. respectively for the fibrinous and serofibrinous form. Primary empyema is said to be more common in children, but expectoration is often absent and an effusion may make the detection of a pulmonary process difficult or impossible.

Secondary Form.—As in other varieties of pleuritis, disease of the lung occupies first place and can be demonstrated in a larger proportion of cases, since the pulmonary lesions leading to suppuration in the pleural sac are more easily detected. Of 252 cases 158 (62.6 per cent.) appeared to be pulmonary in origin, including 140 cases of pneumonia (136 lobar pneumonia, 4 bronchopneumonia), 15 of pulmonary tuberculosis and 3 of abscess or gangrene. Gangrene leads to putrid exudates. The disease may arise by extension from the abdomen, the pericardium, or the other pleura; it may complicate the infectious diseases (influenza, typhoid fever, etc.) or suppurative lesions in any part of the body. It may be caused by trauma and may follow the serofibrinous form. In children empyema is, in general, more frequent than serofibrinous effusion. The younger the child, the more likely is the exudate to be pus. In adults serofibrinous effusions are much more common.

1. *Pneumococcus.*—This appears to be the most frequent organism occurring as a pure infection. Of 137 cases, the pneumococcus was found in 54 (39.4 per cent.). It is the most common cause of metapneumonic effusions, but may also be found in primary empyema and shows a marked tendency to die out. It may be found in smears from the pus, but cultures from the same fluid are not infrequently sterile. To this is probably due the relatively favorable course of pneumococcus empyema. It may be the cause of suppuration in tuberculous empyema, in which tubercle bacilli are found on inoculation, but cultures are sterile from the disappearance of the pneumococcus.

2. *Streptococcus.*—This was present in 28 (20.4 per cent.). Serofibrinous effusions containing streptococci are likely to become purulent.

3. *Tubercle Bacilli.*—This has not been shown to be as frequent a cause of purulent as of serofibrinous effusions. Of Netter's 109 cases, 12 were found to be tuberculous. The finding of other organisms does not exclude the tubercle bacillus nor does the presence of the tubercle bacillus alone exclude other organisms such as the pneumococcus, which may have died out.

4. *Staphylococcus.*—This is relatively infrequent, occurring in only 5 (3.6 per cent.).

5. *Mixed Infections, etc.*—Infection with more than one organism was found in 22 (16 per cent.). The pus was sterile in 25 cases (48.2 per cent.), and infection with the tubercle bacillus or the pneumococcus may be suspected. Other organisms than those already mentioned are uncommon. Influenza bacilli, typhoid bacilli, *Bacillus mucosus capsulatus*, *Streptococcus capsulatus*, diphtheria bacillus, colon bacillus, actinomyces, etc., have been found. Mixed infections are constant with putrid exudates.

Types of the Disease.—The purulent pleurisies have been separated into different groups according to their bacterial etiology, but no dis-

tinctive clinical picture can be formulated for the various forms. It seems best to consider the various infections together and refer to such differences as can be noted under the separate headings.

Pathology.—The pleura is the site of a fibrinous or fibropurulent layer. It is grayish white or yellowish, and may be greatly thickened. The inflammation may be general or circumscribed. The sacculation of fluid is not infrequent. Erosion, ulceration, or even perforation of the visceral or parietal pleura may be found. These destructive processes may be single, but are more commonly multiple and limited to the pulmonary layer. After long-standing empyema, calcification and the formation of bony plates may take place in rare instances.

In fatal cases other organs are seldom uninvolved. Lobar pneumonia, bronchopneumonia, abscess, and gangrene may be the source of the process. After long-standing empyema, chronic interstitial changes may occur about the lung and penetrate the pulmonary tissue along the interlobar septa, the so-called pleurogenous interstitial pneumonia. Suppurative pulmonary lesions and bronchiectasis are likely to coexist. It is often difficult to tell whether the lung is primarily or secondarily invaded. In some instances, pleural suppuration extends to the pericardium, peritoneum, or the mediastinum, from which the opposite pleura may become infected. Endocarditis is not uncommon. The spleen may be large and soft. Thrombosis of intrathoracic or other vessels may be present. Cerebral abscesses may occur. Tuberculosis of the pleura, lungs, or bronchial glands was present in 9 of 38 cases at autopsy in the writer's series. Tuberculous lesions in more remote parts of the body were found in 2. Thus, about 30 per cent. showed tuberculosis in some part of the body.

Location.—Of 248 cases, the right side was affected in 122, the left in 121, and both in 5. Purulent are more often encapsulated than serofibrinous fluids. Encapsulation was discovered in 8 of the present series. When empyema complicates pneumonia, the effusion is usually at the bases irrespective of the site of the pneumonic process.

The Effusion.—No sharp dividing line can be drawn in gross appearance between serofibrinous and purulent fluids. The effusion may be serofibrinous at first and become purulent later. There is often, however, an excess of polynuclear cells in such fluids from the beginning. The fluids may be yellowish, with varying shades of greenish, reddish or even frankly red, brownish or chocolate colored from the presence of blood. With large amounts of pus they are grayish, greenish yellow, or cream colored. They may be without odor, sweetish, or fetid. In gangrene of the lung or pleura they often have a horribly offensive odor. The specific gravity is higher than in serofibrinous fluids. It may reach 1030 or more.

Symptoms.—These are usually the same as in the serofibrinous form and only certain differences need be mentioned. They are not distinctive of empyema. The onset is likely to be more acute. An insidious onset and latent course are less common than in the serofibrinous form. Toxic symptoms are more common and more severe. In general, the temperature is higher; of 145 cases in the writer's series, only 2 ran an afebrile

course. From 101° to 103° is an average pyrexia, but the temperature reaches 104°, 105°, or even higher in a larger proportion of cases, with wider variation between the morning and evening elevations. The respiration and pulse are likely to be more rapid. Recurring chilliness or chills, a more rapid loss of strength and weight and increasing pallor may be mentioned. Between the various infections there are no constant differences. Pneumococcus empyema may be relatively mild. Streptococcus infections are more severe, and putrid exudates are accompanied by most marked disturbances. In the latter, bad taste in the mouth, foul breath, and foul sputum may be present. Uncomplicated tuberculous effusions may run an afebrile and long course without marked general symptoms. In rare instances empyema may persist without symptoms for months or years. In Faisans and Audistère's case the disease may have lasted for forty years. At autopsy there was sterile fluid contained in a space, the walls of which were transformed into cartilaginous and osseous tissue.

Physical Signs.—These are such as have been considered under Serofibrinous Effusion. The affected side may be more prominent, with wider intercostal spaces which may actually bulge. (Edema of the chest wall is uncommon, but more frequent with purulent than with serous fluid. The subcutaneous veins may be dilated. Whispered pectoriloquy (Baccelli's sign) has proved an uncertain differentiation from serofibrinous pleuritis. A disproportion between the amount of fluid and the severity of the symptoms may be suggestive. The displacement of the heart and the liver are relatively greater with purulent than serofibrinous fluid, due probably, to the greater weight of the former. In children the breath sounds may be loud and bronchial over a purulent effusion. The axillary glands are occasionally enlarged on the affected side. The spleen may be enlarged. In long-standing cases, especially in children, clubbing of the fingers may occur.

Pulsating Empyema.—Of 95 cases analyzed by Sailer,¹ 71 had pus in the pleural sac, and of these there was tumor (empyema necessitatis) in 38. In 13 there was intrapleural or extrapleural abscess. The remaining cases were non-purulent or their condition was not definitely known. The condition appears to be more common in males and in early life. Pulsations may be diffuse or localized, single or multiple, and are more often seen on the left side. They are most common in the parasternal regions, but may occur in the lower lateral and posterior parts of the chest. Pulsation is probably due to an accumulation under pressure of fluid which is apposed to a lung made inelastic by collapse or pathological changes in or about it, and to some local or general weakness of the thoracic wall.

The Blood.—*White Cells.*—In 28 cases of primary empyema the white count was above 12,000 in all but 6, and all these cases with a low white count recovered after operation. The white count may be of great value in distinguishing uncomplicated tuberculous serofibrinous effusion from empyema, only 3 of 33 cases with the former showing a white count above 12,000.

¹ *Amer. Jour. Med. Sci.* 1904, cxxviii, p. 225.

Complications.—These are much the same as for serofibrinous pleuritis.

1. *Extension to Neighboring Organs.*—This is more common in empyema. (a) *Perforation of the Lung.*—This may be *latent* and indicated only by the expectoration of mucopurulent sputum. Evacuation of small amounts of pleural pus by this means is frequent. The complication is frequently overlooked and pneumothorax does not occur. In other cases the perforation is *obvious*. In this form pneumothorax is more common, but does not necessarily occur. There is a sudden paroxysm of cough, with the evacuation of a large amount of pus. If perforation occurs while the patient is asleep or if the lung is suddenly flooded, death may take place from suffocation. Single or multiple fistulous tracts may connect the pleura with the bronchi. Invasion of the lung usually leads to multiple abscesses connecting with the bronchi. In some instances the affected lung may present a honey-combed appearance. Single pulmonary abscesses are less common. It is difficult to tell in individual cases at autopsy whether the lung has been primarily or secondarily involved. Of 11 cases with pulmonary suppuration and empyema at autopsy, abscesses were multiple in 8, single in 3. Pulmonary gangrene may occur, but is less common. Chronic interstitial pulmonary changes are likely to follow if the patient recovers. Of 145 cases obvious perforation occurred in 5. One patient recovered. A second had persistent cough, with abundant purulent sputum and frequent attacks of hemoptysis, but was otherwise well, six years after the perforation. The 3 remaining patients died, 1 from suffocation, the others from sepsis. Evacuation by the lung does not obviate the necessity of thoracotomy, which should be done to spare the lung from further damage. Pulmonary perforation may occur at any time, but is uncommon before the third or fourth week.

(b) *Perforation of the Thoracic Wall (Empyema Necessitatis).*—This is less common but more favorable and may be followed by complete evacuation and recovery. The abscess may point in any part of the chest, but more often in the parasternal region or in the fifth interspace outside the nipple line, the thinnest regions of the chest. The perforation may be single or multiple. It seldom occurs before the end of the first month, but may take place at any time after this period. The abscess usually forms an irreducible fluctuating tumor, becoming more tense with forced expiration or cough. It is dull or flat on percussion. The opening into the thorax may be at some distance from the site of the tumor, the rupture of which may be followed by discharge of a large amount of fluid. Forced expiration and cough may hasten, inspiration may diminish to flow. The tumor may pulsate. Evacuation by spontaneous perforation is usually incomplete. The fistula is likely to close, the pleural pus to reaccumulate, with subsequent perforation in the same or other places. Cure by this means is rare and thoracotomy is indicated. Caries of the ribs and necrosis of the soft parts may arise from the perforation. Erosion of an intercostal artery may lead to fatal hemorrhage. Perforation is more common in streptococcus, tuberculous, mixed, or putrid infections. Actinomycosis should always be considered in the presence of abscesses of the chest wall arising by extension from

within. Simple thoracic abscesses may be unaccompanied by pulmonary or pleural changes and are uninfluenced by changes in intrathoracic pressure. The distinction may, however, be impossible before exploration by operation. Suppuration in the tissue between costal pleura and thoracic wall (peripleuritis) leading to external perforation, may simulate encapsulated empyema necessitatis.

(c) *Perforation of the Diaphragm*.—This is more serious. It may lead to local or general peritonitis. As in perforation of the lung, it is often difficult in individual cases to tell whether the infection has spread from the pleura to peritoneum or in the opposite direction. Obvious gross lesion of the tissue may be absent. In other cases the site of the perforation may be readily found. Peritonitis was present in 9 of 38 autopsies on cases of empyema in the writer's series. It was general in 7, localized in 2. In one an encapsulated diaphragmatic empyema pointed in the right hypochondrium; recovery followed operation. An abdominal abscess, starting from the pleura, may perforate the stomach, the intestines, or the kidney. It may extend along the spine to the iliac fossa and simulate psoas or lumbar abscess.

(d) *The œsophagus may be perforated*, with the formation of pleuro-œsophageal fistulæ.

(e) *Infection of the pericardium* is probably more often present than statistics show. It was recognized during life in 4 of 145 cases, but was present at autopsy in 6 of 38. Inflammation may also extend to the mediastinum.

2. *Metastatic Lesions*.—It is uncertain in individual cases whether suppurative lesions in remote parts of the body are primary or secondary. They may arise by extension of the pleural infection to the intrathoracic veins or the endocardium. Cerebral abscesses are among the most dangerous complications, and are usually multiple, as in 3 of 38 autopsies in this series. Pulmonary abscesses were associated in 2. In 1 the cerebral abscesses were unaccompanied by suppurative foci elsewhere than in the pleura. Septicemia is common in empyema.

3. *Amyloid degeneration* may complicate long-continued suppuration.

Causes of Death.—The same danger of sudden death and similar causes obtain in purulent as in serofibrinous effusion. It is uncommon in fatal cases not to find suppurative processes in neighboring or other parts of the body. Peritonitis is one of the most frequent of coincident infections, and was present in 9 of 38 fatal cases, but the complicated character of fatal cases makes it difficult to judge between principal and contributing causes. Pneumonia, pulmonary abscess and gangrene, pericarditis, endocarditis, thrombosis of intrathoracic veins or the auricles, with or without infarction, cerebral abscesses, and meningitis, may be regarded as important factors, either singly or combined. The streptococcus is the most frequent organism, but pneumococci are often present and other organisms may be found.

Relapse.—Recurrence of empyema in the same place after complete recovery does not occur, because of the almost constant obliteration of the pleural sac at this place. Incomplete absorption or removal may, however, be followed by a return of symptoms and an increase in the

amount of fluid. Incomplete evacuation, insufficient drainage, encapsulation, the presence of undiscovered pockets of pus or the development of empyema elsewhere may be responsible for a second accumulation of fluid. Pitt¹ reported the postmortem finding of a smooth pleural surface without adhesions in a child who had empyema one year before.

Sequelæ.—It is rare, on physical examination of patients who have recovered from empyema, not to find signs of the previous disease. There is diminished expansion of the affected side, which often looks smaller, and measurement shows that it is contracted. The interspaces are relatively narrow. Toward the base is slight relative dullness, its upper limit often being highest behind and extending in a nearly horizontal line toward the axilla, where it gradually descends to the inferior pulmonary margin in the anterolateral thoracic region. The extent of dullness is variable and may involve half the chest. The tactile fremitus, breathing, voice sounds, and whisper may be diminished, but are often unchanged. In cases which have run a long course before evacuation takes place, with abundant connective-tissue formation about the lung or within its substance, the lung may be partially or wholly incapable of re-expansion. A space is left which is filled by fibrous tissue by the collapse of the chest wall, dislocation of the mediastinum and heart toward the affected side, displacement upward of the diaphragm and partial expansion of the lung, depending on the changes which have taken place in and about it. In rare cases, with dullness, there may be signs suggestive of slight degrees of pulmonary solidification. These may be due to interstitial changes in the lung, or, if marked retraction has taken place, to proximity of the larger bronchi to the chest wall. In the young, with less resistant thoracic walls, marked deformity with retraction of the side, drooping of the shoulder and lateral deviation of the spine may result.

Pain of variable and usually slight intensity may persist in the affected side. Of 26 patients investigated on this point, 8 still have pain for periods of one to seven years after discharge.

Diagnosis.—The diseases with which pleural effusion may be confused, the differentiation of pleural fluids of different character, the method of employing exploratory puncture and the examination of pleural fluids have been discussed under Serofibrinous Pleuritis. Certain additional features in the diagnosis of empyema may be emphasized.

Exploratory Puncture.—This is indicated if pus is suspected. By hesitation and delay, the disease may be converted into a chronic and incurable affection. In acute cases, with typical signs of fluid, it is practically devoid of danger, and, if present, pus can usually be demonstrated by this means. In some cases it is missed by the needle or is too viscid to flow and a negative puncture does not exclude pus.

Cases in Which Exploratory Puncture is Dangerous.—In cases of empyema of long standing, with contraction of the side, elevation of the diaphragm, and secondary suppuration in the lung, or in cases in which empyema complicates pulmonary abscess, gangrene, bronchiectasis,

¹ *Brit. Med. Jour.*, 1908, ii, p. 1075.

and interstitial pneumonia, the conditions are less favorable for exploratory puncture. The pleural pus is often small in amount, and may be encapsulated between lung and diaphragm or in other parts of the chest. It is well to confirm the results of physical examination by radioscopy. Exploratory puncture is not without danger in cases thus complicated. Bloodvessels lining the walls or traversing the lumen of pulmonary cavities or fresh granulation tissue, if injured by the trocar, have been the source of fatal hemorrhage. Perforation of the elevated diaphragm has caused fatal peritonitis. In such cases, in which from the history, the physical signs, and the x-ray examination there is good reason to suspect pus, the demonstration of which with the trocar has failed or cannot be safely undertaken, it is better to resort to exploratory incision.

Exploratory Incision.—This is indicated when there is good reason to suspect pus which cannot be demonstrated by exploratory puncture or in complicated cases in which it is a less dangerous procedure. It should be entrusted only to an experienced surgeon. The chief danger is artificial pneumothorax, which may arise if the lung is free.

Examination of Pleural Pus. Fluids on the borderline between the serofibrinous and purulent variety may be examined as already indicated in the preceding section. Cultures should always be made. With frank pus, tubercle bacilli may be demonstrated by the following means: A few cubic centimeters are transferred to a flask and diluted with 10 volumes of water. A few drops of strong alkali (KOH or NaOH) are added and the solution is gently heated. After the cellular elements are dissolved, the solution is centrifugized and the precipitate investigated for tubercle bacilli. Animals cannot be inoculated with large amounts of pus or intraperitoneally without a too rapidly fatal termination for the demonstration of tuberculosis. It is best, therefore, to inject only 1 cc. of pus under the skin.

Prognosis.—Absorption of empyema rarely, if ever, occurs. Spontaneous disappearance of pus has been noted in isolated cases and may be due to latent perforation of the bronchi. Recovery may follow obvious perforation of the lung, but usually with most distressing and dangerous complications. After perforation of the chest wall recovery may follow. Most cases, if untreated, end in death. Of 252 cases 56 (22.2 per cent.) died in hospital.

Treatment.—In general, pleural pus should be evacuated as soon as the diagnosis is made. *Constant, free drainage is essential for prompt and permanent cure.*

1. *Thoracotomy with Costatectomy.*—This is the operation of choice. The incision is best made in a dependent part of the pleural cavity, with resection of the seventh or eighth rib in the posterior axillary line. Pus should be evacuated slowly. Irrigation is seldom necessary and may be dangerous. With empyema necessitatis, enlargement of the perforation in the chest wall may suffice if this is in a favorable position for drainage. Otherwise, a second opening in a more suitable position should be made. If pus is encapsulated, the incision must be made where drainage will be most effective. Thoracotomy alone often affords insufficient drainage and costatectomy is often necessary later.

2. *Other Methods.*—These are less efficient since drainage is often neither constant nor free, but may be used in selected cases, as a preliminary to the radical operation or as palliative procedures. Thoracentesis may be considered for effusions on the borderline between the serofibrinous and purulent forms. It is indicated for the evacuation of an exudate of large size, with or without pressure symptoms, as a life-saving measure or a preliminary to operation, thus avoiding the danger of more rapid evacuation, and as a palliative procedure in empyema complicating advanced pulmonary tuberculosis. Although repeated puncture has been advised for pneumococcus empyema, especially in children, it is uncertain, likely to be followed by reaccumulation, and leads to complications and greater deformity of the chest. It frequently delays operation, and subjects the patient to an unjustifiable risk.

Tuberculous Empyema.—In this form the indications are less clear and considerable difference of opinion exists concerning the appropriate treatment. In an advanced stage of the disease a radical operation can hardly be considered, and such palliative measures as repeated puncture or siphon drainage may be tried. The decision is more difficult when empyema complicates early pulmonary tuberculosis. Bäumlér¹ considers that the presence of pyogenic cocci in the exudate demands thoracotomy and best combined with costatectomy, that with tubercle bacilli alone or sterile exudates and pressure symptoms, aspiration may be tried, and if the lung is found capable of expansion, if not too much invaded and the other lung is tolerably free, thoracotomy may be done after some improvement in the general condition. Of 31 cases of tuberculous empyema operated by Küster, 9 recovered, 6 were not cured, and 16 died. In Schede's collective investigation of 45 cases, 10 were cured and 35 died, a mortality of 77 per cent. In general, tuberculous empyema is the most unfavorable form. Of 12 cases, with sterile exudates, in the writer's series, only 1 of whom showed tubercle bacilli in the sputum, 3 died in hospital. Of the remaining 9 patients, 6 have been traced. All have died except 1, who has a discharging sinus, now seven years after operation, but is otherwise well. Sterile exudates are usually, but not necessarily, tuberculous, and in this patient, in whom the empyema was metapneumonic, the process was probably due to the pneumococcus.

After-treatment.—Expansion of the lung may be favored by various devices, permitting the outflow of pus and air through the drainage tubes during expiration, but preventing the re-entry of air during inspiration. A thin layer of impervious material (mackintosh, protective silk) may be applied over the opening of the tubes. The dressing itself, when soaked with secretion, may suffice. A vacuum apparatus may be used as in Perthes' method. After closure of the sinus, respiratory exercises are valuable. Throughout the illness, every means should be taken to build up the general health.

Vaccination.—The subcutaneous inoculation of vaccines may be considered for the treatment of a persistent sinus. Their value must be left for the future to decide.

¹ *Deut. med. Woch.*, 1894, Nrs. 37 und 38.

Results of Operation.—The mortality of the operation itself is very low. In patients near the end, it may hasten the termination, but even in desperate cases, evacuation by some means is justifiable.

SPECIAL FORMS OF PLEURITIS

Diaphragmatic Pleurisy.—Pleuritis may be limited to the diaphragmatic region. It may be partial or general, fibrinous, serofibrinous, or purulent. Large collections of fluid are rare. Owing to its inaccessible site, physical signs are often lacking and the diagnosis may rest on symptoms alone. The pain may present features already described under fibrinous pleuritis, but is more likely to be referred to the lower thoracic or abdominal region. This may be due to implication of the lower intercostal nerve which supply the skin and muscles of the abdominal wall, as well as the parietal and diaphragmatic pleura. In the writer's series, abdominal pain was noted in 5 of 82 cases with primary fibrinous, in 5 of 374 cases with primary serofibrinous, and in 2 of 33 cases of primary purulent pleuritis. It may be associated with muscular spasm and tenderness, and the picture may simulate an acute abdominal affection for which laparotomy has been performed. There may be tenderness over the phrenic nerve in the neck or at the intersection of a vertical line parallel to the outer margin of the sternum and a horizontal line continuous with the termination of the tenth rib (De Mussy's Bouton Diaphragmatique). The breathing may be partially or wholly thoracic and the diaphragm phenomenon absent on one or both sides. Dyspnoea may be marked and attacks simulating angina may be observed (Andral). Obstinate singultus may occur. The phrenic and laryngeal branches of the vagus nerve are implicated and probably through irritation of the former in the diaphragm. The swallowing of food may cause pain.

Encysted Empyema.—Encapsulation of uncomplicated transudates does not occur. It is rare with serofibrinous fluid, but more common with pus. In occasional instances fluid may be serous in one and purulent in another pocket. Sacculation was discovered in only 1 of 1085 cases of serofibrinous effusion, but in 8 (3.2 per cent.) of 248 empyemas in the writer's series. It is, however, probably much more common than these figures show, for in 38 autopsies on patients with empyema it was noted in 12 (31.5 per cent.). Sacculation is more likely to occur in small or medium effusions and in those in which the fluid is at a standstill. Encapsulation may occur between (1) diaphragm and lung, (2) the lung and chest wall, and (3) the lobes of the lung.

1. **Encapsulation of pus between diaphragm and lung** is more common than in other situations. In most instances the empyema is at first free, but is later walled off by adhesion of inflamed and apposed pleural surfaces in the posterior and inferior thoracic region. This was noted in five autopsies. Sacculation of fluid above the diaphragm without apposition to the thoracic wall may occur. The effusion may be bounded by lung and diaphragm, or by lung, diaphragm, and mediastinum. Perforation of lung or diaphragm may be the first objective sign. The

symptoms may suggest diaphragmatic pleurisy. The heart and the organs below the diaphragm may be dislocated, expansion of the affected side may be deficient, and an area of impaired resonance several inches above the base of the lung may be discovered. In this region diminished breathing, voice sounds, and tactile fremitus may be suggestive. Pleuritic friction may occur.

2. Sacculatation between Lung and Chest Wall.—This is not uncommon and likely to occur in cases in which a previous pleuritis has obliterated the diaphragmatic portion of the pleural sac. It is occasionally observed in empyema in which, following operation, the sinus has been allowed to close too quickly. Such encapsulation is more common over the base, but may be observed over other parts of the lung.

3. Interlobar Empyema.—Inflammation of the interlobar pleura occurs as part of a general pleuritis. An effusion of fluid may be limited externally by the thoracic wall, internally by the lobes of the lung between which it lies. In rare instances the effusion may not extend to the chest wall, and is bounded on all sides by the lung. The symptoms are not distinctive and the diagnosis is difficult. The localization of the process in the region of the interlobar septa and the absence of signs above and below this region are most likely to suggest the diagnosis. Examination by means of the *x*-rays may be of great assistance. Sacconaghi¹ has recently reviewed the literature.

Diagnosis.—Laennec regarded ægophony as an important sign. Localized tenderness may be elicited by firm and deep pressure in the interspaces. Sacculated, and especially interlobar empyema, is likely to be confused with pulmonary abscess. Tumors of the lung must also be considered. Exploratory puncture is usually recommended for the diagnosis, but its danger has already been noted, and exploratory incision may be safer. The *x*-rays may be of assistance.

Treatment.—Perforation of the lung has been followed by spontaneous recovery. If perforation has occurred when the patient comes under observation, the decision between an expectant policy and operation must be made on the exigencies of the individual case. If the empyema can be reached, its evacuation is indicated.

Actinomycosis and Nocardiosis of the Pleura.—Two kinds of parasites must be recognized, *i. e.*, *Actinomyces bovis* and the *Nocardia*. Although the two parasites present well-marked biological differences, the clinical and pathological picture in infection is, in general, quite similar.

Actinomycosis.—In a large proportion of the cases this arises by extension from the lung, but may also occur from the œsophagus; by extension downward from the neck to the mediastinum and thence into the pleura; or from abdominal lesions which perforate the diaphragm. Metastasis is a possible mode of origin. The pleura overlying the involved tissue is the site of a fibrinous exudate. A serofibrinous effusion or, more commonly, an empyema may result. Perforation of the chest wall is a characteristic feature. Perforation may take place at any part of the thorax, but is more common in the lower thoracic region. Erosion of

¹ *Gesamt geb. d. prakt. Med.*, 1910, x, 151.

the ribs may occur. Amyloid degeneration may follow long-continued suppuration. Actinomycosis should be suspected in empyema, especially when associated with chronic pulmonary suppuration, interstitial pneumonia, abscess, gangrene, or empyema necessitatis. The diagnosis can be made only by finding granules with branching, Gram-staining filaments and radially disposed club-shaped, eosin-staining peripheral bodies. The prognosis is very unfavorable. A few arrested or apparently cured cases have been reported. The treatment is surgical, combined with the internal administration of large doses of iodide of potassium.

Nocardiosis.—This appears to be much less common. Infection of the pleura takes place by extension from the lung. The changes are similar to those in actinomycosis, and may closely resemble tuberculosis. The diagnosis is made by finding thread-like, branching organisms, which, in most cases, resist decolorization with weak acids and alcohol, but are less "acid-fast" than the tubercle bacillus, do not form granules or masses of closely packed interlacing filaments with the characteristic "clubs" at the periphery and are much more readily cultivated than either tubercle bacilli or actinomyces.

Peripleuritis.—Secondary inflammation of the peripleural tissue is associated with all pleural and many parapleural infections. A primary form has been described, in which, independent of neighboring disease, there is inflammation and suppuration of the tissue between the costal pleura and the chest wall.

Syphilis of the Pleura.—Cases of pleurisy which clear under anti-syphilitic treatment are reported from time to time, but as yet the occurrence of syphilis of the pleura is not established.

Chronic Pleuritis.—1. **Dry Pleurisy.**—This occurs as a sequel to fibrinous, serofibrinous, or purulent pleuritis. Even in the mildest cases of fibrinous pleuritis the pleura rarely escapes some damage. The pleura overlying a pulmonary process may be merely thickened. Adhesions between the pulmonary and parietal layers are common. The pleura may reach a centimeter or more in thickness and enclose single or multiple pockets of serous or purulent fluid. Deposition of lime salts may take place. The neighboring lung is often contracted and fibrous. Bronchiectatic or abscess cavities are frequent. The interstitial pulmonary changes may be due to extension from the pleura, but it is difficult in individual cases to exclude their independent origin. The pleural changes may be simple or tuberculous. In the latter instances, small tubercles, fibrocaseous or calcified areas may be found in the indurated tissue. The site of the process is usually at the bases, when it follows pleurisy with effusion. In tuberculous cases it is frequently at the apices, and extensive pleural thickening may complicate slight pulmonary infections.

There may be no symptoms. Pain of varying and usually slight intensity may be present. Pleuritic friction may exist without subjective symptoms, but adhesions usually prevent the rubbing of the two pleurae together. Chronic apical pleuritis may give rise to depression of the supra- and infraclavicular fossæ, to contraction of the apex, dulness, diminished breathing, voice sounds, and tactile fremitus, but coexistent

pulmonary lesions may make the signs atypical. An apical process is tuberculous in a large proportion of the cases. If pulmonary tuberculosis is suspected, suitable treatment should be instituted. With retraction of the side and fixation of the lung, pulmonary gymnastics will favor expansion and improve the breathing capacity.

2. **Pleurisy with Effusion.**—In rare instances serofibrinous or purulent fluid continues to reaccumulate after repeated thoracentesis or operation.

(a) *Serofibrinous Form.*—Persistent reaccumulation may be due to failure of the retracted and adherent lung to expand and a neglect of early tapping may be responsible. In the absence of malignant disease and obvious pulmonary tuberculosis, a resort to operation may be considered after other measures have been tried. It should be advised with caution, however, for it necessarily induces empyema, which may also fail to heal if the lung is adherent.

(b) *Empyema.*—In this, as in the serofibrinous form, after pus has remained long in the chest, the lung may be partially or wholly incapable of re-expansion from the presence of abundant connective-tissue formation in and about it. After operation and the evacuation of pus, a space is left, and in the young, with less resistant thoracic walls, marked deformity, retraction of the side, and lateral deviation of the spine may result. At times, from the stiffness of its walls, the abscess cavity refuses to close, and cure can be effected only by more extensive operative procedures. In many cases the first operation has been too long delayed. Multiple costatectomy (Estlander's operation) may be considered in persistent partial, but is not likely to succeed in large or total empyema, in the presence of greatly thickened parietal pleura or in old patients with unyielding thoracic walls. In such cases, Schede's "thorax resection" may be successful.

HYDROTHORAX

Transudation of serous fluid into the pleural sacs occurs in the course of many diseases, but when in sufficient amount to be detected during life, is usually secondary to renal or cardiac disease. Renal disease alone gives rise to only small amounts of pleural fluid, but is often combined with cardiac insufficiency. Local stasis is probably a contributing factor with new growths of the pleura, lung, or diaphragm. Occlusion of the azygos veins from pressure or thrombosis is a possible cause.

Cardiac insufficiency may give rise to fluid in one or both pleural sacs, with or without general dropsy. Cardiac hydrothorax is commonly unilateral and right-sided, and when both pleuræ are affected the amount of fluid is usually greater on the right. Of 30 cases of cardiac hydrothorax, the effusion was bilateral in 8, in 6 of which the amount of fluid was greater on the right and equal on the two sides in the remaining 2. It was unilateral and right-sided in 16, and confined to the left side in only 6. The predominance of right-sided accumulations is too constant to be accidental or to be explained by previous pleuritis and obliteration

of the left pleura, which can account for only a small proportion of the cases. Fetterolf and Landis¹ suggest that cardiac hydrothorax is due to pressure on and partial occlusion of the pulmonary veins by dilated portions of the heart. The more common dilatation of the right auricle is responsible for the greater frequency on the right. Hydrothorax from renal disease alone is usually bilateral. If, as often happens, the heart is insufficient, the accumulation may be unilateral and right-sided or double, with an excess on the right. Of 15 cases in the writer's series, the effusion was bilateral in 7, in 2 of which the amount was greater on the right, in 3 on the left, and equal on the two sides in the remaining 2. It was unilateral and right-sided in 6, of which 5 were complicated by cardiac lesions. The effusion was confined to the left side in 2 cases.

If the decubitus is prevailinglly lateral, a larger amount of fluid may collect in the dependent pleura. The pleura may be smooth or slightly clouded and swollen. Old adhesions may limit the accumulation to single or multiple pockets. The fluid is usually clear and yellowish, but may be reddish from admixture of blood. It clots slowly or not at all, and fibrin is absent in uncomplicated cases. The specific gravity in venous transudates is usually from 1010 to 1015, with 1 to 3 per cent. of albumin, while hydræmic fluids are below 1010, with traces of 1 per cent. of albumin. The sediment usually shows an excess of endothelial cells. In rare instances lymphocytes may predominate. A complicating pleuritis is not uncommon, and polynuclear cells may then outnumber the other elements.

Symptoms.—The symptoms are those of the underlying disease. Pain is absent. If there is fever, it cannot be ascribed to hydrothorax. Cough and expectoration may be due to œdema of the lungs. There may be gradually increasing dyspnœa, which may amount to orthopnœa. The signs are the same as with pleural fluid of other character. Pleuritic friction is absent. Shifting dulness is more readily obtained.

Treatment.—This is that of the underlying disease, but removal of the fluid by thoracentesis is indicated, if necessary for the relief of embarrassed circulation or breathing.

HEMORRHAGIC PLEURAL FLUIDS

Microscopic blood is always present in pleural fluids. Small amounts may arise from puncture of the lung in thoracentesis. Larger quantities of fresh blood color the fluid reddish or even blood red. Dieulafoy estimates that 5000 to 6000 red cells per cc. are necessary to give the fluid a definitely red color. Only cases with frankly hemorrhagic fluid are considered here. In old extravasations the fluid may be reddish brown, yellowish, or greenish. Clinically, it is convenient to divide bloody fluids into hemoserotherax (hemorrhagic pleurisy), hemohydrothorax, and hemothorax.

Hemoserotherax (Hemorrhagic Pleurisy).—**Primary.**—(a) *Tuberculous.*—An apparently primary disease of the pleura with the production

¹ *Amer. Jour. Med. Sci.*, 1909, cxxxviii, p. 712.

of serohemorrhagic fluid is tuberculous in a great majority of cases. (b) *Malignant*. In a relatively small proportion of cases it is due to carcinoma, rarely sarcoma. (c) *Simple Hemorrhagic Pleurisy*. There is no sound pathological evidence in support of this group as a primary affection, although hemorrhagic fluids of secondary and infectious origin are not uncommon. The clinical cases with an apparently primary hemoerotherax of simple origin, practically always run a clinical course consistent with tubercle or malignant disease, or show one or the other of these conditions at autopsy. There are a few striking exceptions as regards a more favorable clinical course. Cheesman and Ely¹ reported a most remarkable instance in a woman, aged forty-seven years, with bloody fluid in the right, then in the left chest, and finally, following the disappearance of this fluid, with bloody serum in the abdomen. The pleural accumulations continued for about eighteen months. The abdominal fluid ceased to reaccumulate after about five years. In all, two hundred and seventy-nine pints of fluid were removed.²

Secondary.—This is a much more common form. Cases due to tuberculosis, although they may seem clinically to be primary, are usually secondary. So, also, in hemorrhagic pleurisy due to malignant disease, the primary form is rare, that from metastasis relatively common. Cases not included in these two groups may be classed, as in the primary form, as simple hemorrhagic pleurisy. Hemorrhagic serofibrinous effusions of this sort are perhaps most common in pneumonia, and are usually due to the pneumococcus. Of 57 cases of croupous pneumonia, showing pleural effusion at autopsy in the Massachusetts General Hospital, in 6 the exudate was bloody. In none of these was there evidence of tuberculosis of the pleura. An inflammation of the pleura in the course of malignant fevers (variola, typhoid) in purpura hemorrhagica or complicating such asthenic conditions as accompany malignant disease, nephritis, cirrhosis of the liver or chronic heart disease, may be of the hemorrhagic variety, whatever the cause of the process in the pleura. Some prove to be tuberculosis; others are simple and due to the pneumococcus or pyogenic organisms, the blood in the exudate being due to passive congestion or the intensity of the local process. An interesting feature of the hemorrhagic pleural fluids is the high percentage of eosinophiles which they may contain and the presence, also, of a large number of eosinophiles in the circulating blood. In a case of apparently primary disease of the pleura in the writer's series, the bloody pleural fluid showed no excess of eosinophiles, but contained enormous numbers of cholesterol crystals, while the systemic blood showed 6400 white cells, of which 20 per cent. were eosinophiles.

Hemohydrothorax.—Transudates may have a hemorrhagic character in cardiac or renal disease. Thrombosis of the thoracic veins or their occlusion by pressure of tumors is a possible cause.

Hemothorax.—This may be due to the rupture of intrathoracic vessels following the development of aneurysm, their erosion by disease

¹ *Amer. Jour. Med. Sci.*, 1899, cxviii, 162.

² The writer is informed that the patient is entirely well twenty-three years from the onset.

or injury by trauma. In the rupture of the aorta or its ulceration the left pleura is more often the site of the hemorrhage. The pulmonary veins and the vena cava may rarely be the source. The rupture of pulmonary vessels from destructive pulmonary processes may rarely lead to hemorrhage into the pleural sac. The intercostal arteries may likewise be eroded in disease of the pleura. There is a specimen (No. 2159) in the Warren Museum from a patient with empyema, in whom erosion of an intercostal artery led to fatal hemothorax.

Traumatic Hemothorax.—**Etiology.**—This may arise from contusions of the chest, fracture of the ribs, and incised or penetrating wounds. Owing to the protected position of the intercostal arteries, their injury is relatively uncommon. In a large proportion of cases the hemorrhage is from a wound of the lung, superficial injuries of which may lead to varying and usually insignificant hemothorax, deeper wounds to abundant hemothorax, if an important vessel is involved. The injury of vessels accompanying bronchi of the second or third order may be followed by hemorrhage compatible with survival.¹ Wounds of vessels about the hilus of the lung and the larger mediastinal vessels are rapidly fatal.

Pathology. Following the injury of the larger bloodvessels, fatal hemorrhage into the pleura may occur within a few minutes. An effusion of blood from the parietal vessels and the lung usually begins at once and is slowly continuous. In the more favorable cases the bleeding usually stops after twenty-four to forty-eight hours. Delayed hemorrhage is rare. Coagulation of the effused blood invariably occurs. It is frequently noted that hemorrhagic pleural fluid does not coagulate on removal, and this is probably due to its previous coagulation within the chest. In favorable and uncomplicated cases the fluid is wholly absorbed. The blood clot becomes adherent, softening and organization take place, and after small extravasations, nothing but a few adhesions may remain. With large hemorrhages and much clot, more extensive adhesions and thickening of the pleura persist. The blood is not in itself a cause of pleuritis, and when infection occurs it is due to bacteria which have invaded the pleural sac from without, through the thoracic wound or the lung. It is less frequent in small effusions, and less likely to occur following injuries of the parietal vessels or the superficial parts of the lung, without an external wound. Large effusions, those arising from incised or penetrating wounds, and hemorrhage from the deeper parts of the lung, often become purulent. Hemorrhagic pleural effusion following trauma may rarely be tuberculous.

Symptoms.—In small and slowly accumulating effusions there may be no symptoms. Shock is a variable feature. Pressure symptoms usually occur within twenty-four and are rarely delayed for forty-eight hours. In one of Nélaton's cases the hemorrhage was delayed for thirty-six days. With the rapid accumulation of a large amount of blood, death may ensue within a few minutes. In most cases there

¹ Nélaton, "Des épanchements de sang dans les plèvres, etc.," *Thèse de Paris*, 1880.

is slowly increasing dyspnoea, which is the most constant symptom, due to collapse of the lung and consequent dislocation of the mediastinum. Pain may be present, and is usually referred to the affected side. Cough is an inconstant symptom. If the lung is wounded there is likely to be hemoptysis. Blood in the sputum may consist of blood streaks, or there may be frank hemoptysis. In addition, with the more rapid accumulation, there are symptoms due to loss of blood, pallor, progressive elevation of the pulse, with alteration in its quality, coldness of the extremities and body, and sweating. Syncope or delirium may occur. The temperature may be subnormal at first, and in favorable cases may not exceed normal limits. In a considerable proportion of cases the temperature rises, after the first or second day, a degree, a degree and a half, or even two degrees Fahrenheit, and remains thus elevated for several days. Although such an elevation of temperature naturally occasions much anxiety, such cases not infrequently progress favorably. The rise in temperature may be due to absorption. The physical signs differ in no respect from those of other pleural fluids.

Complications and Sequelæ.—Infection of the effused blood is most to be feared. There are no trustworthy statistics, but it appears from Nélaton's 94 collected cases that the effusion became purulent, with more or less certainty in 21. Hemopneumothorax is common, and may become pyopneumothorax. Pneumonia, pulmonary abscess, or gangrene may arise from the injury or follow as a result of empyema.

Diagnosis.—A careful physical examination should be made when the patient first comes under observation. A neglect of this precaution may lead to unnecessary delay in the diagnosis of an empyema. A pleural effusion developing within a few hours of a thoracic injury means hemothorax with practical certainty; a delayed effusion is usually inflammatory, rarely hemorrhagic. The early detection of infection is most important. Evidence of its occurrence is usually afforded by elevation of temperature, which commonly takes place from the third to the fifth day, and is accompanied by other symptoms of sepsis, which may develop only after days or weeks have elapsed. The presence of an infection may be suspected when, even without fever, there is a delay in the absorption of the fluid, which in most cases progressively diminishes in amount, and moderate effusions may be fully absorbed within a month. Any increase of a fluid which has previously reached a standstill should likewise be regarded as due to inflammation and not recurrent hemorrhage, which is relatively uncommon. An enumeration of the white cells in the systemic blood at intervals may be of value in the early recognition of suppuration. An initial leukocytosis may be due to hemorrhage alone.

Exploratory puncture and the withdrawal of sufficient fluid for diagnosis should be done if empyema is suspected. If the puncture is made at a distance from the original injury there is less danger of dislodging an occluding thrombus. The needle should be inserted toward the upper rather than the lower level of the fluid, to avoid a dry tap from penetration of the clot. If properly performed, and under rigidly aseptic precautions, it is practically devoid of danger. An infection may be

sufficiently obvious from inspection of the fluid. In developing or mild infections microscopic examination of the sediment may show an excess of polynuclear cells and also that degenerative processes are at work from their necrotic appearance. Cultures should be taken.

Prognosis.—Traumatic hemothorax is always serious. The site, extent, and character of the original injury, the rapidity with which the hemorrhage takes place and the amount of effused blood are important factors. In some cases the effusion may be small, and pneumothorax may be the significant feature. To these dangers that of infection is added. Of Nélaton's 94 cases of traumatic hemothorax, gathered from the older literature, 49 died from immediate or remote causes. The seriousness of chest injuries, in general, can be gathered from the cases collected from the literature by Garré.¹ In 37 cases of pulmonary rupture the mortality was 63 per cent., in 100 cases of punctured wounds, 38 per cent.; in 535 bullet wounds, 30 per cent. Hemorrhage, pneumothorax, and infection are the principal causes of death.

Treatment.—The cases come within the province of the surgeon. Aside from the surgical care of external wounds an expectant policy should be followed in cases without alarming symptoms. The patient should be absolutely at rest. Immobilization of the affected side by strips of adhesive plaster may favor cessation of the hemorrhage. The administration of lactate of calcium, 15 gr. (1 gram), four times a day, may be of value. The hemothorax if uninfected will be absorbed. If suppuration occurs, the empyema should be opened and drained. The large proportion of deaths from hemorrhage, from suffocation by hemothorax or pneumothorax, and the frequency of plural infection leave much to be desired from surgery in the care of such cases.

Although the cleaning and disinfection of external wounds may be secured, and doubtless eliminates a small measure of infection, there still remains the considerable danger of infected material already carried into the thorax or arising in consequence of a communication between the lung and the pleura. In cases with alarming symptoms and for the present as a life-saving measure, a more active surgical intervention may properly be considered. A source of the hemorrhage in a parietal vessel may at times be determined from the site of the injury. The lung itself is, however, more often the source, and then surgery is less likely to be successful. The lung is likely to be partly or wholly collapsed and the bleeding wound difficult to find or to reach. Suture of the lung has as yet been too infrequently performed to furnish trustworthy statistics.

CHYLOTHORAX

Chylous and Chyliform Pleural Fluids.—Much confusion exists in the classification of milky fluids which accumulate in the serous sacs. Quincke,² in 1875, grouped the cases into those with chylous fluid (hydrops chylosus) in which the appearance was due to the presence of true chyle,

¹ *Archiv f. klin. Chir.*, 1905, lxxvii, p. 209.

* ² *Deut. Arch. f. klin. Med.*, Band xvi, pp. 121 to 139.

and a second class with fluid of a chylous appearance (hydrops chyloformis seu adiposus), the milky character being due to cells undergoing fatty degeneration. The distinction is often difficult and at times impossible. The two types of fluid may be present in different cases, both of which are due to a similar cause, and a single sample of fluid may likewise present features common to both. The differentiation from the presence of sugar cannot be relied upon. Rotmann¹ believes that sugar is a differential sign of importance only when present in an amount exceeding 0.2 per cent.

Such fluids are white and milky, but may be reddish from the presence of blood or show varying shades of yellow or green. In the last instance they may readily be mistaken for purulent fluid. They are usually odorless, but may be slightly sweetish. Thin layers are opalescent. On standing a creamy layer of fat collects at the surface. They are resistant against putrefaction. Their milky appearance is maintained after filtration or centrifugalization, but they can be cleared by shaking with ether. From 0.06 to 3.71 per cent. of fat has been extracted. The amount of albumin is variable; from 3.36 to 7.37 per cent. has been reported, with traces of casein in one instance. Solids are present from 5 to 10 per cent., inorganic substance (salts and extractives) about 1 per cent. Fibrin is variable—present in some, absent in other cases. Cholesterin, lecithin, calcium, magnesium, potassium, sodium, chlorine, and carbonic, sulphuric, and phosphoric acids have been found. Microscopic examination discloses a large number of minute fat droplets about the size of micrococci. In the chylous fluids the fat granules are very numerous, with only few formed elements, while the chyloform fluids contain less numerous fat granules, of larger size, and more numerous cells in different stages of fatty degeneration.

Pseudochylous Fluids.—Pleural fluid without fat may have a milky appearance. Quinke showed that albumin in fine subdivision may cause a milky appearance. Lion,² in 1893, showed that fat was absent in a milky abdominal fluid which he studied. An albuminous body was found, the nature of which was uncertain. Such substances have been regarded as lecithin, globulin, casein, or a compound of globulin and lecithin. These pseudochylous fluids are distinguished from the chylous and chyloform fluids by the separation of the latter into two layers on standing, while the former remain homogeneous. The microscopic examination of chylous or chyloform fluids shows the presence of fat, which may be stained black with osmic acid or removed on shaking with ether. In gross appearance, chylous and chyloform fluids may resemble purulent fluids.

Occurrence.—Chylous or chyloform pleural fluids are of infrequent occurrence. It is probable that they are more common, however, than the number of reported cases indicates, since chylous may be readily confused with purulent fluid, unless carefully examined. Bargebühr³ was able to collect 41 cases, reported from 1633 to 1894, an incidence

¹ *Zeit. f. klin. Med.*, 1896, xxxi, p. 416.

² *Archiv de méd. expériment.*, 1893, No. 6, p. 826.

³ *Deut. Arch. f. klin. Med.*, 1895, 54.

of 1 case reported about every six years. Rotmann in 1896 brought the number to 49.

Etiology.—Of 40 cases in Rotmann's series, in which the cause could be determined, 27 were classed as chylous, 13 as chyloform. Of the chylous cases, 8 were due to trauma; 5 to cancer of the pleura; 4 to occlusion of the left subclavian vein. Two cases were ascribed to each of the following causes: compression of the duct by tumors, disease of the lymph vessels (sclerosis, lymphangiectasis), and malignant lymphoma, and 1 case to each condition as follows: occlusion of the thoracic duct, excessive exertion and parasites (*filaria*?). The presence of chyloform fluid, with admixture of fatty degenerated cells, was due to cancer of the pleura, lymph vessels, etc., in 5; tuberculous pleuritis in 3; exudative (non-tuberculous) pleuritis in 3; and pulmonary abscess(?) in 1. One case was regarded as the result of an abnormal amount of fat in the blood (lipemia?).

Diagnosis.—Pleural fluid of a chylous or chyloform character can be determined with certainty only by an examination of the fluid. It may be suspected, however, following trauma, with malignant disease of the pleura, glands, or lymphatics, and with thrombosis of the left subclavian vein. The association of pleural fluid with the known presence of chylous ascites may suggest a chylous character to the former. Uncomplicated cases of chylous or chyloform pleural fluid are usually afebrile. Such an accumulation may occur at any age and in either or both pleural sacs.

Prognosis.—*Chylous Fluids.*—The transudation of chyle into the pleura adds to the danger of the underlying disease, from the additional tax on the patient from the loss of food which would otherwise be utilized in the system. Thus the course of an affection steadily progressing toward a fatal termination may be hastened. The rapidity and extent of the accumulation are important; small accumulations, the removal of which is unnecessary, add little to the danger of the original disease. The prognosis becomes more unfavorable when the frequent recurrence of alarming pressure symptoms necessitates the repeated withdrawal of large amounts of chylous fluid. The underlying cause is usually of so grave a nature that in general the prognosis must be considered unfavorable. Of 22 cases (11 classed as chylous, 11 probably chylous) in Rotmann's series only 4 recovered. Of these, 2 were due to trauma, 1 to probable disease of the lymph vessels, and the last to an uncertain cause.

Chyloform Fluids.—The prognosis is more nearly that of the underlying cause, such cases being due to fatty degeneration of existing cells.

In cases with chylothorax in which recovery has followed it is probable that the chylous transudation has come from branches of the main thoracic duct or that the occlusion of the latter is compensated by an abundant collateral circulation. Slight lesions of the thoracic duct may heal and the duct remain patent.

Traumatic Chylothorax.—Such cases present features of special interest from their rarity and more favorable prognosis. Of 11 cases recorded in the literature, the chylothorax was double in 1 (Henssen), left-sided

with right hemothorax in 1 (Handmann's first case), right-sided with left pneumothorax in 1 (v. Thaden), and confined to the right side in the remaining 8 (Quincke, Kirschner, Krabbel, Helferich, Handmann, Hahn, Dietze, and Lindstrom). The traumatic cases may be fatal from the original injury plus the mechanical effect of the pleural fluid, or in time from loss of lymph.

In 1 of the reported cases (Dietze) an injury to the thoracic duct followed a self-inflicted bullet wound. In the remaining cases the chylothorax was due to severe mechanical injury to the thorax, with certain or probable fracture of the ribs. In 2 of the 5 fatal cases the thoracic duct was found to have been injured by fragments of the tenth and eleventh dorsal vertebræ respectively. The mechanism of the injury to the duct in the other cases is uncertain. It may have been lacerated or ruptured by bony fragments of the ribs or vertebræ, or compressed between the mediastinal structures and the vertebral bodies with sufficient force to injure it, without injury to the more resistant neighboring structures (aorta, azygos vein, œsophagus). In these cases the implication of the parietal pleura in the injured structures is indicated by the presence of chylous fluid in the pleural sac. Rupture of the thoracic duct may, however, lead to an accumulation of chyle outside the pleural sac provided the parietal pleura is uninjured. Under these circumstances the mediastinum may be infiltrated or the parietal pleura dissected up from the thoracic wall, as in Eyer's case.

Treatment. This presents a somewhat different problem from other pleural fluid, since the diminution of pleural pressure favors reaccumulation and changes in pressure interfere with the healing of lesions of the lymphatic vessels. The repeated loss of large amounts of such fluid is a severe drain. It is best, therefore, in the presence of small amounts of fluid to keep the patient under observation after sufficient material has been withdrawn for diagnosis. Strapping the affected side may prevent an increase of the fluid by diminishing the respiratory changes in intrapleural tension. When an excessive amount of fluid has accumulated it must be evacuated with the trocar. If possible, operation should be delayed until the level of the fluid has ceased to rise. It is better to remove small amounts frequently than a large amount at one time. Because of the inaccessible site of the thoracic duct an attempt at its ligation is hardly likely to prove successful. An increase of intrapleural pressure to that of the atmosphere, following resection of a rib, may effect a cure. Thoracotomy was followed by recovery in one case (Helferich) and death in another (Lindstrom).

TUMORS OF THE PLEURA

A. Benign Tumors.—These are rare and without a distinctive clinical picture. They usually run their course undetected and are first discovered at autopsy. In general they consist of tumors arising in neighboring organs which invade the pleura by encroachment, usually remaining extrapleural, at times projecting into the pleural space, but enveloped by its visceral or parietal layer.

Aberrant lung tissue may project into pleural space. In a case described by Muus,¹ a smooth tumor the size of a walnut was found in the left pleural cavity, attached to the diaphragm and covered by diaphragmatic pleura. The tumor showed on section an alveolar arrangement. Small single or multiple cysts of the pleura are described by Stilling² and Zahn.³ Their walls contained cartilage and acinous glands, lined with ciliated epithelium, suggesting their origin from the bronchi. Emphysema may give rise to cyst-like structures projecting into the pleural cavity (bullous marginal emphysema). A specimen in the Warren Museum (No. 2142) shows such a bleb, the size of a horse-chestnut, its walls composed of thickened pulmonary pleura, lined with delicate trabeculae and connecting with the bronchi. They may reach a much larger size. Their rupture may give rise to pneumothorax. Pulmonary adenoma, angioma, or osteoma may invade the pleural sac. Fibroma may arise in the lung and similarly invade the pleura.

Lipoma.—Fatty tumors may rarely arise from the subpleural fatty tissue and project into the pleural sac. They are usually too small to give rise to symptoms or physical signs, and are discovered postmortem, growing from the costal, diaphragmatic, or mediastinal fatty tissue as rounded or flattened, sessile or pedunculated masses. Fitz⁴ has reviewed the literature and reported a case. In rare instances, lipoma of the thoracic wall may communicate with the subpleural space and project into the pleural sac. Such possible communication through the thoracic wall with the thoracic cavity should be borne in mind in operations for the removal of subcutaneous lipomas, as infection of the wound may readily lead to infection of the pleura.

B. Primary Malignant Disease.—1. **Carcinoma.**—Although the term endothelioma has been most commonly applied, carcinoma seems more appropriate. The general character and histological appearance of the tumor do not, in general, sufficiently differ from carcinoma in other regions, and its origin in the surface epithelium or lymph-vessel endothelium is too uncertain to warrant a more distinctive term.

Occurrence.—This is a rare affection, of which some 40 to 50 cases are sufficiently well recorded to permit of acceptance.⁵ The writer has had opportunity of studying sections from 3 cases.⁶ It is probable that the condition has not infrequently escaped detection because of the readiness with which it may be confused with chronic pleuritis, without a microscopic examination of the tissue. The disease is more common between forty and fifty years, but the ages of the reported cases vary from ten to seventy-four years. Men are somewhat more frequently affected. In rare instances it has followed trauma to the chest wall.

¹ *Virchow's Archiv*, clxxvi, p. 180.

² *Ibid.*, Band cxiv, p. 557.

³ *Ibid.*, cxliii, pp. 173 and 416.

⁴ *Transactions of the Association of American Physicians*, 1905, xx.

⁵ Cases reported to 1897 have been collected by Glockner, *Zeit. f. Heilkunde*, 1897, xviii, to 1905, and by Bloch, *Les Néoplasmes malins primitifs de la plèvre*, Paris, Vigot Frères.

⁶ Two among 2000 autopsies at the Massachusetts General Hospital, a third and unpublished case of S. D. Wolbach's.

Pathology.—The disease is usually unilateral and occurs about equally on the two sides, although the right pleura has been somewhat more commonly involved. Rarely both pleuræ are invaded. The entire pleura of one side may be increased in thickness to 1, 1.5, or even to 2 cm. In other cases only a part of the pleural sac is diseased. The affected region is usually diffusely invaded, is gray or grayish yellow in color, and studded with discrete to confluent white, grayish or yellowish nodules, varying in size from a pinhead to a pea. More rarely the pleura is the site of larger multiple and isolated masses of growth. At times there are no nodules; the pleural surface is merely uneven and apparently diffusely involved. The tissue is hard and tough on section. Ulceration is not found. Adhesions are common. A variable amount of bloody, less commonly serous, rarely purulent fluid is usually present.

Metastases have been observed in the supraclavicular (Fränkel and Bonheim), the axillary glands (Neelsen), and the thoracic muscles (Neelsen, Perls, Pirckner, Glockner, and Schulz), spontaneously or along the needle track, after withdrawal of pleural fluid (Podack and Scagliosi). The disease has usually invaded other organs when death occurs. The most frequent site of secondary deposits is in the lungs. The bronchial, tracheal, mediastinal, retroperitoneal, and mesenteric glands, the viscera, other serous membranes, etc., may be the site of metastases. In six of the reported cases (Wagner, Böhme, Teixeira de Mattos, Benda, Scagliosi, and Bonheim) no metastases were found. In the presence of carcinoma elsewhere than in the pleura, and especially with the disease in the lungs, it is never certain that the pleural disease is primary.

Symptoms.—The disease usually begins like an ordinary pleuritis, and in its course closely resembles pleural tuberculosis. Pain is usually a prominent symptom and is often increased by a long breath and cough. Dyspnoea and cough are not usually striking features at first, but may be present without invasion of the lung. In the presence of pleural fluid, dyspnoea may be extreme and orthopnoea may be present. If the lung is involved the sputum may contain blood. Fever is usually absent. Loss of flesh and strength are usually progressive.

An accumulation of pleural fluid is almost constant and the physical signs are such as are commonly found with pleural fluid from other causes, although certain additional features may permit a probable diagnosis. The progressive loss of flesh and strength will naturally suggest a severe affection. The absence of signs pointing to disease in the apices of the lungs, the failure to find tubercle bacilli in the sputum, and the afebrile course may argue against tuberculosis; a negative tuberculin injection may positively exclude it. The presence of metastases in accessible regions may be an important sign. Inoculation metastases in the course of the needle track are especially important and suggestive and should always be sought in suspected cases. They are usually small, flat, hard, slightly movable, and painless. Invasion of the needle track with tuberculous material from the pleura may likewise occasionally give rise to similar nodules and thus their excision and microscopic examination may be necessary to establish the diagnosis.

On examination of the thorax, diminished expansion of the affected

side may be a striking feature. During the early part of the disease the side may be more prominent, to appear somewhat smaller later, with relatively narrow and less depressed interspaces. With effusion, the heart may be displaced, returning at first to its former position after the withdrawal of the fluid. As the new growth gradually invades a larger territory and as the pleura becomes thicker and less elastic, with the formation of adhesions, the heart often fails to return to a position which it might be expected to assume after the removal of such an amount of fluid. For similar reasons, the thoracic distress and sense of pressure are afforded progressively less relief from the evacuation of the fluid, which reaccumulates more rapidly. The operator may also be able to appreciate the much thickened and tough pleura by the resistance offered in the introduction of the trocar. The physical signs may show little if any change after the removal of even large amounts of fluid.

Examination of the *pleural fluid* may afford important data for diagnosis. It is often serous at first, becoming blood-tinged or even strongly hemorrhagic after the first or the first few tapplings. This is due to the inelastic character of the pleural walls, and probably, too, as examination of sections shows, to the not infrequent presence of bloodvessels near the free surface of the pleura, from which under the influence of increased negative pleural pressure following removal of the fluid, blood is readily extravasated. With the progress of the disease and the frequent repetition of tapping the fluid may resemble pure venous blood or have a chocolate color. That its bloody character is associated with the use of the trocar is suggested by the more frequent bloody character of the fluid in cases in which fluid has been withdrawn and the occurrence of serous fluid in cases which have been allowed to run their course without such interference. Careful chemical examination of the pleural fluid has not been made. The specific gravity, when taken, has usually been 1018 or under. Microscopic examination of the sediment may assist in a decision between malignant disease and tuberculosis. In carcinoma of the pleura there is usually a much larger proportion of endothelial cells, with a relatively small proportion of lymphocytes, the cytological formula thus conforming to that in fluids due to stasis. There is no reason to believe that the large cells, with vesiculated nuclei and vacuolated protoplasm, not infrequently found in plaques, are other than desquamated cells from the free surface of the pleura. The presence of many cells showing typical or atypical mitoses has been thought diagnostic of malignant disease. It may rarely happen that the microscopic examination of a small piece of tissue removed with the needle may establish the diagnosis.

Prognosis.—The disease usually terminates fatally within six months of the discovery of the pleural invasion but may last for eighteen to twenty months.

Treatment.—This is largely symptomatic. Removal of the pleural fluid usually affords only temporary relief. At times it has been followed by marked improvement, especially in the early stages of the disease. As the disease progresses, distressing pressure symptoms usually necessitate more frequent withdrawal, and not infrequently with less and less

relief. At times, with much thickening of the visceral pleura, removal of fluid may only aggravate the symptoms from increased tension on a retracted and adherent lung. Morphia is of value and may prolong the intervals between the tapplings. It is better to withdraw small amounts frequently than to empty the cavity at each tapping.

2. **Sarcoma.**—Primary sarcoma is even less common than primary carcinoma in the pleura. Although in some of the reported cases a distinction has not been made between the two groups, this is justified from the general character and histological appearance. Thirteen cases are reported, and only 1 case has come under observation of the writer.¹ Nine of these 14 cases occurred in males. The ages varied from seven to seventy-six. Of the remaining patients, 2 were from ten to twenty, 4 from twenty to thirty, 2 from thirty to forty, 1 from forty to fifty, 2 from fifty to sixty, and 1 from sixty to seventy. The two sides are about equally affected. In their clinical course they resemble primary carcinoma of the pleura. A collection of pleural fluid practically always accompanies the new growth, and this is usually bloody, rarely serous. Its hemorrhagic character may first appear only after tapping. The presence of spindle cells in the sediment may suggest spindle-celled sarcoma of the pleura, as in Warthin's case.

In gross character at autopsy, primary sarcoma of the pleura usually presents a different appearance from primary carcinoma. In rare instances, however, as in primary carcinoma, the pleura may be diffusely and homogeneously invaded. Rarely, there are innumerable small nodules, but the new growth is commonly single, hard, or soft, its surface smooth or lobulated, in color white, gray, or reddish, of variable and usually considerable size, even at times reaching that of a man's head. The pleura may cover the growth which appears to arise in the subserous tissue. In other cases no traces of pleura can be found, and the tumor itself forms the lining of the pleural sac, yet ulceration is uncommon. Invasion of neighboring organs by extension or metastases in the lungs, the neighboring glands, ribs, vertebræ, liver, spleen, or superficial parts of the body has occurred. In three cases no metastases were found.

C. **Secondary Malignant Disease.**—Malignant disease of the pleura is more commonly secondary than primary. The tissue may be invaded by metastases from a primary malignant tumor in any part of the body, but pleural invasion is more common in malignant disease of the lung, mediastinum, thoracic wall, or stomach. Metastatic new growths of the pleura do not usually produce a diffuse infiltration of the tissue; there are commonly several isolated nodules or masses, and more rarely the pleura presents a generally nodular appearance. Pleural fluid may or may not be present, and this may be serous, but is more commonly bloody. In cases of pleural carcinoma secondary to the disease in the

¹ Twelve cases will be found referred to and summarized in Bloch's *Les Néoplasmes malins primitifs de la plèvre*, Paris, Vigot Frères, 1905. Cases of Bernard, Blumenau, Brunati, Dumarest, Hofmohl, Israël-Rosenthal (two cases), Kaufmann, Ménadière, Młodziewsky, Percy-Kidd and Habershon, and Regnault. A thirteenth case is reported by Warthin (*Medical News*, October 16, 1897). The writer has had an opportunity of studying an unpublished case of H. A. Christian's.

breast, the clinical picture, course, and termination may resemble primary carcinoma of the pleura.

Of 178 cases coming to autopsy at the Massachusetts General Hospital with carcinoma in various regions, 10 showed secondary deposits in the pleura. Of 10 cases with carcinoma of the breast, the pleura was invaded in 4. Of 58 cases in which the disease was primary in the stomach, only 3 showed pleural metastases. In this series, carcinoma of the pleura was also secondary to the disease in the thymus and ovary. Of 42 cases of sarcoma, primary in various regions, the pleura was secondarily invaded in 9.

ECHINOCOCCUS DISEASE OF THE PLEURA

Etiology.—Following the ingestion of the egg of *Taenia echinococcus*, the embryo, liberated from its shell in the stomach, may migrate to the pleura. The course pursued is uncertain, but the more frequent infection of the right pleura suggests a migration by way of the portal blood stream or biliary channels to the liver, thence through the diaphragm to the pleura. Infection may be direct or by way of the lymph channels or the systemic circulation.

Pathology.—It is convenient to divide cases into those in which the disease apparently arises within the pleural sac or the pleural tissues: (A) *Pleural Echinococcus*: The difficulty of distinguishing cysts of the pleura from those developing in their neighborhood and the frequency with which the latter lead to disturbances in the pleura, justifies a further division of cases into (B) *Parapleural echinococcus*, in which the primary infection has taken place in a neighboring organ, but in its growth the cyst encroaches upon the developments at the expense of the pleural space.

(A) **Pleural Echinococcus.**—(a) **PRIMARY.**—The exact site of the primary infection is uncertain, as cases come under observation with the cysts already developed to a considerable size. The number of cases in which the disease is primary in the pleura is small. In the combined statistics of Neisser and Madelung, among 1179 cases, echinococcus was primary in the pleura in only 18 (1.5 per cent.). This report is based on 43 cases.¹ The right pleura was involved in 25, the left in 10; in 8 the site was not given.

¹ Neisser, *Die Echinococcus Krankheit*, Hirschwald, Berlin, 1877, 17 cases; Madelung, *Beiträge zur Lehre von der Echinococccen-Krankheit*, Stuttgart, 1885, 2 cases; Maydl, *Ueber Echinokokkus der Pleura*, Wien, 1891 (cases 8, 9, 11), 3 cases; Theophil Rosenthal, *Diss.*, 1881 (quoted from Winzerling), 5 peripleural cases; Winzerling, *Ein Beitrag zur Casuistik des primären Pleurachinococcus*, *Inaug. Diss.*, Jena, 1892, 3 cases; Mosler and Peiper, *Nothnagel's Spec. Path. u. Ther.*, Band vi, 1 case mentioned; Ascoli, *Rendiconto della Società Lancisiana* (quoted from Orlandi), 4 cases; Vannini, *Bulletino delle scienze Mediche di Bologna*, 1896, p. 240, 1 case; Pasca, *Rendiconto Società Lancisiana degli Ospedali*, Roma, 27 giugno, 1896, 1 case; Orlandi, *Gazzetta medica di Torino*, 1898, 49, 1 case; von Bokay, "Festschrift" in honor of Abraham Jacobi, New York, 1900, 1 case; Cary and Lyon, *Transactions of the Association of American Physicians*, 1900, xv, 1 case; Belehmaan, *Ueber primären Echinococcus der Pleura*, *Inaug. Diss.*, Kiel, 1901, 1 case; Hauser, *Primärer Echinococcus multilocularis der Pleura und der Lunge mit entwicklung multipler Metastasen im Gehirn*, Erlangen u. Leipzig, 1901, 1 case; Ransom and Willis, *British Medical Journal*, 1903, i, 302, 1 case.

The cyst is usually situated at the lower, but may be confined to the upper part of the pleural cavity. The local reaction leads to the formation of a connective-tissue envelope, which is usually very thin, but may be thick. Pleuritis is uncommon. Enlargement of the sac gradually compresses or displaces neighboring organs. Perforation may occur into the lungs with evacuation through the bronchi; or erosion of the ribs and intercostal spaces may lead to rupture through the chest wall. Both are rare. The cyst may become infected, and presents the appearance of an encysted empyema. The most common type is a single cyst or one sac containing daughter cysts (endogenous echinococcus). Rarely more than one cyst is found. A pleural cyst with multiple external budding (exogenous echinococcus) is described by Cary and Lyon, and an alveolar echinococcus (*Echinococcus multilocularis*), apparently primary in the pleura and with coincident or metastatic multilocular cysts in the lung, the diaphragm, psoas muscle, and brain, is reported by Hauser. The localization of cysts in the peripleural tissue, between the costal pleura and the thoracic wall, is difficult to determine. Their separate consideration is hardly justifiable, as they probably represent cysts arising in the pleural or subpleural tissue, the development of which toward the lungs is prevented by dense adhesions.

(b) SECONDARY.—1. *By Metastasis*.—It is still an open question whether an echinococcus cyst, primary in the pleura, can give rise to metastases in other and remote parts of the body. It is likewise uncertain whether unruptured cysts in parts distant from the pleura can lead to secondary pleural invasion. The weight of opinion is rather that multiple and isolated cysts are due to infection with more than one *Taenia echinococcus* embryo,

2. *By Extension*.—Auto-infection through rupture of the mother cyst, the evacuation of daughter cysts into neighboring tissues and their further development is established for abdominal echinococcus. A similar secondary infection of the pleura from the rupture of pulmonary or hepatic cysts may take place, but pleural infection with bacteria usually precedes or so quickly follows that without operation, death almost always occurs within a variable and usually short period.

(B) **Parapleural Echinococcus**.—(a) *Intact Cysts*.—In this class may be included cases in which the disease develops in neighboring organs, but encroaches upon and grows at the expense of the pleural space. The cases comprise for the most part those in which cysts are present in the peripheral parts of the lung, the upper part of the liver, or the region between the liver and the diaphragm; and more rarely echinococcus disease of the mediastinum, spleen, or kidney. The clinical picture may be quite indistinguishable from primary pleural echinococcus. Subdiaphragmatic and especially hepatic cysts are most common and the diaphragm may be elevated to the second rib and even to the clavicle. In both the subdiaphragmatic and pulmonary forms of the disease the heart may be displaced laterally, the liver dislocated downward. The condition of the pleura in the presence of an echinococcus cyst in its neighborhood is variable and depends to some extent on the presence or absence of suppuration in the cyst. The visceral and parietal layers

may be free, serous or purulent pleural fluid may be present, but partial or complete adherence of its layers is more common and more favorable, as rupture of the cyst may then fail to infect the pleura.

(b) *Perforated Cysts*.—According to Neisser's statistics, echinococcus disease of the liver breaks through into the respiratory apparatus in about 11 per cent. of the cases. Disturbances of the pleura from parapleural echinococcus are more common than from the primary disease. Depending on the previous condition of the pleura and the character of the cyst contents, rupture is followed by free or encysted, cystic, serous, or purulent fluid. Suppuration is practically a constant feature. The perforation of an adherent pleura with invasion of the lung or bronchi is most common. Of 30 cases in Davaine's series only 9 ruptured into the pleura, 21 into the lung or bronchi. In Neisser's 60 cases the pleura was invaded in 16, the lung in 12, and the bronchi in 32. Hepatopleural or hepatobronchial fistulæ may result, and bile may be found in the pleural cavity or even be expectorated. An echinococcus cyst of the lung may likewise lead to free or encysted and usually purulent pleural fluid, following rupture. If the pleuræ are adherent the pulmonary cyst may evacuate externally. Rupture into the bronchi is more common.

Symptoms.—In rare instances there may be no symptoms. In cases in which the disease is primary in the pleura the symptoms are usually those of a slowly growing intrathoracic tumor. Cough may be absent or present, with scanty mucoid sputum from an accompanying bronchitis. Dyspnœa is usually present and is progressive. There may be pain with respiration, but this is not a striking feature unless pleuritis is present. Fever is usually absent. Emaciation is not common in uncomplicated cases. The perforation of pleural cysts into the lung is rare. Septic pneumonia and even abscess and gangrene may follow. If there is free communication with the bronchi, clear cystic fluid may be expectorated. In this or in evacuated pus, hooklets or bits of cyst membrane may be discovered. Rupture may occur through the chest wall, following atrophy of the intercostal muscles and erosion of the ribs. Spontaneous rupture is likely to occur if the cyst has suppurated. The perforation of parapleural echinococcus into the pleura is less common than into the lung. Rupture may take place without symptoms; in other cases the patient may be conscious of the rupture, which is followed by pain of a severe character, and if suppuration is present, as is commonly the case, there is chill and fever. Rupture may be spontaneous, or may be induced by exertion or trauma. Hepatic echinococcus cysts may perforate the pleura and be evacuated through the lung without characteristic elements in the sputum in case the bile passages fail to connect with the cyst.

Urticaria may follow the rupture of pleural echinococcus into the pulmonary or other tissues or of parapleural cysts into the pleura. Severe symptoms of intoxication, even delirium, collapse, and death may likewise follow the rupture.

The duration of pleural echinococcus is difficult to determine. To judge from its growth in accessible regions it may take from six months

to a year for it to reach the size of the fist. Symptoms may arise only after it has attained a large size.

On examination the signs are usually those of encysted pleural fluid. There is diminished expansion of the affected side, which is likely to be prominent, with obliteration of the normal intercostal depressions. The side may be dull or flat on percussion, and in some cases it is possible to note an irregular or evenly curved arching of the upper border of dullness, the convexity of which is directed upward. The tactile fremitus and breathing are diminished or absent; the latter may have a bronchial quality. The voice sounds are diminished and ægophony may be present. The signs are likely to be atypical. Between the involved area and the lung there may be an abrupt transition on auscultation to normal vesicular breathing. In the presence of a large cyst fluctuation may possibly be made out, but the hydatid fremitus or quivering of jelly sensation has not been observed. The liver or spleen may be displaced downward, the heart to the right or left. The presence of echinococcus cysts elsewhere in the body may suggest a similar affection of the pleura.

Blood.—The presence of eosinophilia in the circulating blood may be confirmatory. Cabot collected 30 cases of hydatid of the liver, only 2 of which were negative. Of 20 cases in Welsh and Barling's series all but 5 exceeded the average in health.

Diagnosis.—Infection with echinococcus is rare in North America and Great Britain, and cases which occur are for the most part in foreigners. A previous residence where the disease is prevalent, and contact with dogs used for herding sheep, may be suggestive. Positive data for diagnosis are furnished by the discovery of scolices, hooklets, or cyst membrane. If perforation has occurred into the lung, such material may be present in the expectoration. An urticarial rash following thoracentesis is very suggestive. The examination of the fluid obtained by pleural puncture may furnish suggestive chemical features. It is usually clear, transparent, and varies from 1009 to 1012 in specific gravity. Sodium chloride is present. Albumin is usually absent or present only in traces. Traces of inosit, succinic acid, and grape-sugar may be found, and although suggestive, are not distinctive of the disease. In some cases the specific gravity is high and the amount of albumin considerable. If degeneration has taken place, cholesterin crystals may be found. If infection has occurred, it may mask the appearance of the fluid. Specific antibodies in the blood of patients with echinococcus disease may be demonstrated by the complement fixation test. The antigen may be made from the cyst fluid or an alcoholic extract of the cyst membrane. Kreuter¹ has reviewed the literature.

A resort to thoracentesis for the diagnosis of pleural or pulmonary echinococcus is attended by considerable danger, for perforation of the enveloping connective-tissue sac and the cyst membrane may result in the evacuation of the cyst fluid into the pleura or the lung if erosion of its substance has already occurred. As the perforated cyst membrane is subjected to changes of intrathoracic pressure with respiration

¹ *Beitr. z. klin. Chir.*, Band lxxvi.

or cough, the contained fluid may find its way between connective-tissue envelope and cyst membrane to the bronchi. Urticaria, symptoms of severe intoxication, with gastro-intestinal disturbances, faintness, collapse, delirium, and even coma, and death may result. Pulmonary or pleural suppuration or suffocation from mechanical obstruction by fluid or cysts may occur. Maydl reports 11 cases of pleural or pulmonary echinococcus in which a fatal result followed thoracentesis. When we consider the infrequency of the disease, this is a warning which cannot be safely disregarded. If the diagnosis can be made without puncture it is better to resort to operation without previous exploration. If thoracentesis is done, a small trocar (not a needle) is less dangerous, and if the case proves to be echinococcus, operation should be at once undertaken.

The pleural, pulmonary, or subdiaphragmatic site may be difficult to determine and the different forms may coexist. In Patella's case¹ the diagnosis before operation was pleural, after operation hepatic, and at autopsy pulmonary echinococcus. Centrally placed pulmonary cysts may be without signs. The cyst is usually single and in the lower lobes, more commonly the right. When signs are present with a cyst in the peripheral parts of the lung the signs are usually the same as in pleural echinococcus. Pain is less often present, dyspnoea may be more paroxysmal, cough is likely to be more troublesome, and the sputum may be bloody. Rupture into the bronchi is more common in pulmonary than in pleural cysts. The differentiation is often impossible during life, and even at autopsy it may be uncertain whether the growth started in the lung or pleura. Subdiaphragmatic cysts which may be confused with the pleural or pulmonary form usually involve the liver at its upper part or the space between liver and diaphragm. In either case the diaphragm is elevated, the lung compressed, the heart displaced to the right or left, and the liver depressed. The clinical picture may resemble pleural echinococcus, but the depression of the liver and the lateral dislocation of the heart are less marked. Cough may be absent and dyspnoea less troublesome. The greater vertical excursion of the lower pulmonary margin and the presence of the diaphragm phenomenon, with subdiaphragmatic cysts, may be important differential signs. The distinction between an intrathoracic and intra-abdominal cyst is important for surgical interference.

Of pleural diseases, echinococcus may be confused with benign or malignant new growths and encysted or free pleural fluid. Of malignant disease, the secondary pleural carcinoma or sarcoma can usually be excluded by the presence of a primary focus elsewhere. In primary malignant disease the course is more progressively downward, with loss of flesh and strength. Superficial metastases may be found. Pain is a more prominent symptom. Owing to the diffuse character of the process, the whole or a greater part of one side of the chest may be dull. The percussion note is more board-like, and if free fluid is present its upper border may show a characteristic curve. In the later stages of

¹ Quoted from Maydl, *loc. cit.*, p. 71.

malignant disease the affected side is more often somewhat contracted. If inflammatory fluid is present there is often the history of an acute onset with pain and fever. There may be evidence of pulmonary or other disease to which the pleural fluid is secondary. The pain is likely to subside as the fluid accumulates. Such processes seldom last as long nor does the accumulated fluid as slowly and steadily increase. With free fluid the line of demarcation between it and the lung is less abrupt than in echinococcus disease, the upper limit of flatness may have a characteristic curve, and changes in level may be made out on changing the position of the patient. If encysted fluid is purulent, its character may be suggested by symptoms of sepsis. The appearance, chemical character, and microscopic examination of fluid obtained by puncture afford valuable data for differential diagnosis. Urticaria following exploratory puncture should suggest echinococcus disease.

Prognosis.—This is practically hopeless for cases of echinococcus cysts of the pleura or the parapleural tissue rupturing into the pleura, and allowed to run their course without treatment. Of 31 unoperated cases in Neisser's "statistics," including 12 pleural, 7 pulmonary with pleural perforation, and 12 hepatic with pleural perforation, all died. The prognosis is much worse for pleural than pulmonary echinococcus, in which perforation into the lung may be followed by recovery. The prospect in operated cases is much more encouraging. Of 13 operated cases of pleural echinococcus in Maydl's statistics, 4 (30 per cent.) died.

Treatment.—Evacuation of the cyst contents with the trocar, with or without the injection of solutions containing iodine or other substance, has been followed by cure, but is uncertain and too dangerous to recommend. The high mortality following puncture of the cyst has been mentioned. A radical operation only can be considered. Costectomy is better than simple incision. If possible, the cyst should be removed without rupture. If too large to be removed entire, the cyst membrane may be drawn into the wound of operation and aspirated. It may then be shelled out from its capsule. As it is often difficult to be certain that the cyst is not pulmonary or subdiaphragmatic, the pleura should be carefully approached. If suppuration of the sac has taken place, the abscess should be opened and drained. Subdiaphragmatic cysts projecting into the thorax are best approached through the pleura.

CHAPTER XXIX

PNEUMOTHORAX

By FREDERICK T. LORD, M.D.

By this is understood the presence of atmospheric air or gas in the pleural cavity. There is frequently also a liquid exudate, hence the terms hydropneumothorax with serous, pyopneumothorax with purulent, and hemopneumothorax with bloody fluid.

Historical Note.—The splashing sound produced by succussion is mentioned in the works commonly ascribed to Hippocrates, and is frequently spoken of as "Hippocratic succussion," but the condition in which it was noted was regarded as empyema, the distinction between empyema and pneumothorax not being clearly appreciated. A few cases were described, usually of the traumatic variety, and the mechanics of pneumothorax were fairly understood in the seventeenth and eighteenth centuries, but the thesis of Itard¹ in 1803 is commonly regarded as the starting point of the modern conception of the disease. Itard named the condition Pneumothorax, and recognized its relation with tuberculosis. In 1819 Laennec published the most important contribution up to that time. He described the causes, symptoms, and physical signs, and his account of the auscultatory phenomena left practically nothing to be added by those who have since written on this subject. He was the first to give the succussion splash its true significance. Emerson,² in 1903, published the most elaborate and complete treatise on the disease, and here may be found an abstract of many important articles. Renewed interest has recently been aroused in artificial pneumothorax as a therapeutic measure in the treatment of pulmonary tuberculosis.

Pathological Physiology.—An appreciation of the mechanical factors is essential to a clear understanding of pneumothorax.

The thorax is capable of rhythmic changes in volume during inspiration and expiration. Inspiratory enlargement is accomplished by the contraction of muscles applied to the bony frame-work and the descent of the diaphragm. Within the thoracic cavity the lungs in communication with the atmosphere through the trachea hang free and unattached, although everywhere in close apposition to its walls. Since the pleural sac is without communication with atmospheric air and since the lungs are easily distensible, with each inspiratory enlargement of the chest air enters the trachea and inflates the lungs much as one fills a hand-bellows with air by separating its handles. The lungs are not only easily

¹ Dissertation sur le pneumothorax ou les congestions gazeuses qui se forment dans la poitrine, Thesis, Paris, 1803.

² Pneumothorax: an Historical, Clinical, and Experimental Study, *Johns Hopkins Hospital Reports*, 1903, xi.

distensible but are elastic and are stretched in both phases of respiration beyond the volume they would assume if the pleural cavity was open and in free communication with the external air. Expiration is passive and due to the elastic recoil of the lungs and the thoracic and abdominal walls. Owing to the constant elastic tension of the lungs there is in the potential pleural space a negative pressure which is greater during inspiration than in expiration.

Many attempts have been made to measure this normal intrapleural tension after death in man and on living animals, but the results of such observations cannot be regarded as indicating the condition in healthy man. The most trustworthy figures appear to be those of Aron,¹ who found as an average of 36 observations the maximum reading for quiet inspiration -5.09 and the minimum for expiration -2.54 mm. Hg. in a healthy individual willing to allow a manometer to be inserted into the chest. This normal tension thus demonstrated probably varies within wide limits in different individuals. In the fetus and the newborn the lungs fill the chest even after the pleural space is perforated and there is no pressure difference, which first shows itself with increasing growth, probably because the thorax grows more rapidly than the lungs.² Pleural adhesions or disease in the lung and mediastinum are also likely to influence the pleural pressure and may serve to explain the wide differences obtained in the measurement of intrapleural tension by different observers and in the clinical behavior of cases of pneumothorax.

The contention of West³ that between the pleural surfaces a cohesive force exists sufficient to overcome the pulmonary elasticity has been the subject of much controversy. Those who uphold this view maintain that the so-called normal negative intrapleural tension has no real existence, but is latent and first manifest only when the pleural surfaces are separated in an effort to demonstrate it. To Brauer⁴ the negative pressure determined by the manometer in the normal pleura is a symptom of pneumothorax. No conclusive evidence for or against this hypothesis has yet been offered.

Owing to the elastic tension of the lung and the consequent negative pressure in the potential pleural space the admission of air to the pleural cavity is followed by the collapse of the lung. The mechanical conditions differ somewhat, depending on whether the communication of the pleural space with the outside world is open, valvular, or closed.

Intrapleural Pressure in Pneumothorax.—Observations are not numerous. Among them Aron (*loc. cit.*) reported three cases illustrating each form. In a patient operated on for empyema with an open external fistula the pressure oscillated about the zero point, with an average of -2.62 mm. Hg. during inspiration and $+1.01$ during expiration. In a case of valvular pneumothorax, the average pressure at the height of inspiration was $+7.93$ mm. Hg., during expiration $+10.48$. In a patient with closed pneumothorax the pressure in inspiration was $+0.4$, in expiration $+5.0$.

¹ *Die Mechanik und Therapie des Pneumothorax*, 1902.

² Hermann, *Pflüger's Arch.*, 1879, xx, 365.

³ *Brit. Med. Jour.*, August 20, 1887.

⁴ See Mosheim, *Beiträge z. Klinik der Tub.*, 1905, iii.

A positive pressure at the height of inspiration as in this case suggests the diagnosis of closed pneumothorax. Among West's¹ 20 cases of pneumothorax the highest pressure was 9 inches of water (17 mm. Hg.).

Incidence.—The cases occur more commonly in early adult life, between twenty and thirty, corresponding to the period when pulmonary tuberculosis is most frequent. The condition is occasionally observed in children, but is rare under three years of age. It may occur as the result of trauma in efforts to resuscitate the newborn. Males are more frequently affected, probably because subjected to greater physical exertion. Among Drasche's² 198 cases, 158 were males. In James's³ series of 125 cases, 103 were males. Statistics vary as to the frequency with which the two sides are affected. It seems to be somewhat more common on the left.

Etiology.—There are three groups: (1) The air may come from a perforation of the pulmonary pleura and the lung, bronchi, trachea, œsophagus, stomach, or intestines, forming an internal fistula. (2) Air may gain entrance to the pleura through a perforating wound of the outer chest wall, forming an external fistula. In both groups atmospheric air is admitted to the pleura. (3) Gas may be generated by decomposition of a pleural exudate and without demonstrable external or internal fistula.

The commonest cause is disease of the lung, and in the great majority of the cases there is tuberculosis. Among Biach's⁴ 918 cases from three Vienna hospitals, 715 (77 per cent.) were due to pulmonary tuberculosis. Of Weil's⁵ 55 cases, 46 (84 per cent.) were tuberculous. In Drasche's⁶ 230 cases, 198 (86 per cent.) were ascribed to this cause; of Mosheim's⁷ 50 cases, 42 (86 per cent.). Thus from 80 to 90 per cent. may be regarded as tuberculous.

The incidence of pneumothorax among patients with pulmonary tuberculosis was 36 (10.1 per cent.) among 355 cases which came to autopsy in Weil's (*loc. cit.*) series. West⁸ estimates it as 5 per cent. of the fatal cases. In large series of clinical cases the proportion is lower, as among Drasche's⁹ 10,212 cases of pulmonary tuberculosis in which there were 198 (1.93 per cent.) with pneumothorax.

Pneumothorax occurs more often in active than in latent, inactive, or arrested tuberculosis. Most cases are due to the rupture of small subpleural tubercles which break down before communication with the pleural cavity is prevented by the formation of adhesions. Its infrequency in connection with large cavities and the more chronic types of the disease is due to the more extensive and firmer pleural adhesions in these forms. The apex of the lung, though the most common site

¹ Intrapleural Tension, *Allbutt's System of Med.*, 1899.

² *Wien. klin. Woch.*, 45 and 46, 1899.

³ Osler's *Mod. Med.*, first edition, vol. iii, p. 870.

⁴ Zur Aetiologie des Pneumothorax, *Wien. med. Woch.*, 1880, xxx.

⁵ *Deut. Arch. f. klin. Med.*, May 30 and July 13, 1882.

⁶ *Wien. klin. Woch.*, No. 45, 1899.

⁷ *Beiträge z. Klinik der Tub.*, 1905, iii.

⁸ A Contribution to the Pathology of Pneumothorax, *Lancet*, May 3, 1884.

⁹ *Wien. klin. Woch.*, No. 51, December 21, 1899.

of cavity formation, is seldom the seat of the rupture, owing to the frequency with which pleural adhesions obliterate the pleural sac in this region. Rupture of the pleura may occur during a violent effort, as coughing, lifting, or sneezing, but in many cases there is no apparent immediate cause and the patient may be at rest in bed. In 23 cases with sudden onset at the Massachusetts General Hospital the pneumothorax occurred while the patient was sitting still or in bed in 14.

Of other diseases of the lung in which pneumothorax may occur, abscess or gangrene and bronchiectasis as a group stand next in frequency, but the cases are rare. Pulmonary infarction may be the underlying cause. Bach¹ reports 3 cases and collected 31 from the literature in which emphysema was a certain or probable cause. There were 15 autopsies, and pulmonary tuberculosis was present in 5. Tumors of the lung and echinococcus disease are rare causes. Abscess and hydatid disease of the liver, ulcer or cancer of the stomach, cancer of the œsophagus, and perforation of the œsophagus by a fish bone have been recorded as causes of pneumothorax. Spontaneous erosion and perforation of the lung or the chest wall by an empyema in rare instances cause pneumothorax.

Pneumothorax may be caused by a *penetrating wound* of the chest wall or of the lung such as stab or gunshot wounds, but it is surprising how seldom this complication occurs. Among 21 cases of penetrating wounds of the chest in Bach's series there were no instances of pneumothorax. Otis² states that pneumothorax was a troublesome complication in less than a half-dozen cases among the vast number of chest wounds during the war. In fractures of the ribs a fragment of bone may injure the lung and produce pneumothorax. In James' series of 127 cases 11 were due to this cause. Occasionally a marked concussion of the body may rupture the lung and thus cause pneumothorax without external wound or fracture of a rib. Hemothorax is a frequent complication in traumatic pneumothorax. Empyema operated in the ordinary way is converted into open traumatic pneumothorax.

The operation of *thoracentesis* may be responsible. A considerable number of cases have been reported. Sears³ in 1906 was able to find references to 50 cases. Injury to the lung by the point of the instrument is rarely a cause. Faulty technique and the entrance of air through the cannula or needle is common, radiographic examination not infrequently indicating the presence of pneumothorax after the partial aspiration of pleural fluid. The amount admitted in this way is ordinarily small and no unfavorable symptoms usually ensue. The use of an air-tight trocar diminishes this danger. Misapplication of the tubing to the aspirating pump of Potain's apparatus so that air under positive pressure is blown into the chest has caused immediate death. The rupture of pleural adhesions, an emphysematous vesicle or superficial pulmonary cavity by an excess of negative pressure during the aspiration of pleural

¹ Ueber das Vorkommen des spontanen Pneumothorax bei Emphysem, *Beiträge z. Klinik d. Tub.*, 1910-11, xviii, p. 21.

² *Medical and Surgical History of the War of the Rebellion*, part i, vol. i.

³ *Amer. Jour. Med. Sci.*, 1906, cxxxii, p. 850.

fluid is probably the most common cause of the more serious types of pneumothorax in this group. It has been assumed that the reduction of pleural pressure by aspiration may liberate gas from the pleural blood-vessels and give rise to a so-called "pneumothorax ex vacuo." Although the possibility of this must be admitted in a cavity with rigid walls, yet the amount of gas must be small and of no practical importance.

There is a small group of cases in which pneumothorax occurs in apparently healthy individuals after some unusual exertion, at times after laughing, crying, coughing, sneezing, or yawning, and in rare instances while at rest and even asleep. There may be nothing in the history or physical examination to suggest tuberculosis and the pneumothorax is rarely complicated by an effusion. This is the so-called spontaneous or idiopathic pneumothorax. Fussell and Riesman¹ reported 2 and collected 56 cases from the literature. Young adults are most frequently affected. Death rarely follows and the pathology is not definitely known. Latent tuberculosis, the rupture of an emphysematous vesicle or the tearing of pleural adhesions are to be considered in explanation. The frequency of tuberculosis as a cause of other types of pneumothorax makes it necessary to exclude it more rigorously than has hitherto been done before any other explanation can be accepted. In cases in which other evidence of tuberculosis is lacking, negative tests should be obtained with sufficiently large doses of tuberculin before the non-tuberculous character of the disturbance can be regarded as established.

Finally there are a few cases in which pneumothorax appears to be due to the development in pleural fluid of a gas-producing organism. In Levy's² case, Fränkel's anërobie gas-producing organism was found; in May and Gebbard's³ case an unidentified gas-producing organism; in Hamilton's⁴ the *Bacillus aërogenes capsulatus*; and in Finley's⁵ the colon bacillus.

Pathology.—If there are no pleural adhesions and the opening into the pleura is large, the lung collapses and retracts to a varying degree toward the root and may be found at autopsy as a more or less shrunken mass lying against the spinal column. In long-standing cases it may be tough, fibrous, and practically airless, with little resemblance to the normal lung. Areas of tuberculosis with cavity formation are usually present. Pleural adhesions may bind the lung at one or more places to the chest wall over a greater or less extent. In some instances air is confined to a portion only of the pleural space, giving rise to partial pneumothorax. Confinement to an interlobar space without contact with the periphery of the lung was observed at autopsy in the case reported by Monnier.⁶ Such instances are extremely rare.

The perforation can usually be demonstrated without trouble and commonly leads into a large or small tuberculous cavity at the periphery of the lung. The hole may be several centimeters in diameter or so

¹ *Amer. Jour. Med. Sci.*, August, 1902.

² *Arch. f. exper. Path. u. Pharm.*, 1895, xxxv, p. 335.

³ *Duel. Arch. f. klin. Med.*, 1898, lxi.

⁴ *Montreal Med. Jour.*, December, 1898.

⁵ *Ibid.*, 1899, xxviii, 759.

⁶ *Gaz. méd. de Nantes*, November 2, 1907.

small as to be invisible and first discovered only after the inflated lung is submerged in water. The perforation is usually single, but in rare instances two or more are found. In Roe's¹ case a left-sided pneumothorax was due to perforation of the right lung through an adherent mediastinum. In some instances, an inflammatory exudate occludes the perforation, converting an open into a closed pneumothorax.

Experiments on animals and observations on man have shown that air alone does not act as an irritant to the pleura, but since pneumothorax usually arises under conditions in which bacteria readily gain entrance to the pleura, it is only in exceptional instances, such as spontaneous pneumothorax or in rapidly fatal forms, that pleurisy fails to complicate the process. A fluid exudate usually forms, and according to West² is serous, seropurulent or purulent each in about one-third of the cases. Purulent exudates are common in children and following rupture from the alimentary canal. Hemothorax is not infrequent in traumatic cases.

Displacement of the thoracic and abdominal organs takes place and usually to a degree proportional to the amount of air and fluid in the pleura. The mediastinum and the heart are moved to the opposite side unless held by adhesions. According to James' (*loc. cit.*) observations and contrary to the general impression, the heart is not rotated or swung from its point of attachment at the root of the great vessels, but carried bodily across to the opposite side, its long axis maintaining about its normal relation to the long axis of the body. Encroachment on the sound lung follows the displacement of the mediastinum. Dislocation of the heart is greater with left than with right-sided processes. The diaphragm is depressed on the affected side at times to such a degree that it projects downward and presents a convex surface toward the abdomen into which the movable viscera are also crowded. The position assumed by the heart and abdominal organs is well shown in the accompanying plates from photographs taken at autopsy. (See Plates XIX and XX.)

Symptoms.—Sudden onset is relatively uncommon. In 68 of Saussier's³ 196 cases it was with violent pain and dyspnoea. Of 64 certainly or probably tuberculous cases at the Massachusetts General Hospital the onset was sudden in 23. Much depends on the local conditions. The initial symptoms are most severe when there are no pleural adhesions and the lung and mediastinum are free from disease, permitting complete collapse of the lung and dislocation of the mediastinum toward the sound side. The most alarming onset is therefore likely to be observed in early tuberculous cases, in traumatic or in spontaneous pneumothorax. Noteworthy symptoms are usually lacking when it occurs as a complication of empyema rupturing through the lung or following thoracentesis for the removal of pleural effusion.

Symptoms when present are most commonly pain in the affected side and sudden and severe or rapidly progressive dyspnoea. In uncomplicated cases there is slight and unproductive cough. If there is con-

¹ *Med. Times and Gaz.*, April 7, 1866.

² *Lancet*, 1887, i, 1264.

³ Thesis., Paris, 1841.

PLATE XIX



Pyopneumothorax—Right Side. (James.)

PLATE XX



Pyopneumothorax—Left Side. (James.)

siderable purulent material in an infected lung more abundant sputum may follow its expression from pulmonary cavities or the bronchi. The rupture may be felt as in Stokes'¹ case or it may even be audible to the patient as reported by Banks.² The symptom complex may simulate angina pectoris. In Beardsley's³ case with extensive left pneumothorax there was sharp, severe pain with muscular spasm in the left side of the abdomen suggesting peritonitis, but none was found at autopsy.

A typical severe attack like the following is occasionally observed. Thus, in a person previously in apparent good health there may be sudden, sharp pain in the chest, an immediate intense feeling of suffocation and fear of impending death, air hunger, and great restlessness; the face at first pale and later cyanotic; the hands and feet cold and blue; the skin bathed in cold sweat. The *alæ nasæ* dilate, the respirations are rapid, and the accessory muscles of respiration brought into play. The patient is usually found in the sitting position and if able to speak may plead in a weak and scarcely audible voice to be taken to the open window. The pulse is rapid, small, feeble, or imperceptible. In 5 of 83 cases (Massachusetts General Hospital) the attack was followed by unconsciousness, which terminated in death in one instance.

In milder cases there may be only slight pain and an increase of dyspnœa, the patient meanwhile not being incapacitated. In four cases (Massachusetts General Hospital) the succussion splash was the first intimation to the patient and the principal symptom of which he complained. In the majority of cases the occurrence of pneumothorax leaves no striking impression on the clinical aspect or is indicated only by an aggravation of existing symptoms. This is due to its usual occurrence late in the course of pulmonary tuberculosis when the lung is already considerably involved and the pleural sac partially obliterated by adhesions. In many cases the condition is unsuspected and discovered only in the course of the routine physical examination.

Signs.—These are commonly striking and distinctive. Small amounts of air may readily escape detection, however, and be first noted in the *x-ray* examinations.

Inspection.—Immediately following the entrance of a large amount of air into the pleura the patient usually finds the sitting or half-sitting position most comfortable. In rare instances, as in Garde's⁴ remarkable case, the knee-elbow position is assumed, probably to prevent the disturbances incident to backward displacement of the heart. In this instance it was maintained for about fifty-six days (!). The decubitus in the more severe cases is likely to be on the affected side. Immobility, distension, flattening or fulness of the intercostal spaces, and absence of the diaphragm shadow may be noted. Weil reported œdema of the hand on the affected side, Zahn,⁵ of the chest wall. Subcutaneous emphysema, at times of an extreme grade, is occasionally seen in traumatic

¹ *Diseases of the Chest*, 1837.

² *Dublin Quart. Jour. Med. Sci.*, 1854, xvii.

³ *New York Med. Jour.*, 1911, xciii, 529.

⁴ *Arch. gén. de Méd.*, 1828, xvii, 345.

⁵ *Virchow's Arch.*, 1891, 123.

cases or following thoracentesis. Dislocation of the heart away from the affected side is an important early sign and may be indicated by a visible cardiac impulse to the right or left of its normal position, the displacement being most marked in left-sided cases.

Palpation.—Vocal fremitus is much diminished or abolished over the involved region. In 70 of James' series in which this was noted above the level of fluid, it was diminished in 52 and absent in 18 cases. Vocal fremitus is usually absent over fluid. With a large amount of air the intercostal spaces may be felt to be wider than on the unaffected side. Palpation may also establish the position of the displaced cardiac impulse and that of the depressed liver or spleen. Depression and inversion of the diaphragm can hardly be determined by palpation alone.

Mensuration.—This may show enlargement of the affected side, but the side may look larger, and this fail of confirmation with the tape or the affected side may measure less than the other.

Percussion.—The percussion note is largely dependent on the size, shape, and tension of the air-holding cavity, the position of the retracted lung, the presence of adhesions, character of the pneumothorax, whether open or closed, and the presence or absence of fluid. The condition of the pleura appears to have no striking or constant influence on the percussion sound and it is sometimes difficult or impossible to explain variations in different cases or in different parts of the chest. The percussion note is usually strikingly loud, of low pitch, and may be described as hyperresonant and such as is obtained over an emphysematous lung. If the pneumothorax is large and the pleura free from adhesions hyperresonance may be determined to extend beyond the limits of the normal lung, exceeding the middle line toward the unaffected side over the mediastinum and invading or abolishing the hepatic or splenic dulness. The cardiac dulness also disappears or changes its position. In open pneumothorax there may be a tympanitic note. In some cases the resonance is defective or dull. The percussion note may have an amphoric quality.

With total pneumothorax, the retracted lung lies along the spine and is not demonstrable by percussion, but if adhesions bind it over a larger or smaller extent to the chest wall the percussion note is impaired over the adherent area. Defective resonance from this cause is frequently demonstrable at the apex, may be found along the spine posteriorly, and at times in other parts of the chest. The occasional presence of areas of tympanitic resonance below the level of fluid may be due to pleuritic adhesions.

Other modifications are at times observed. A cracked-pot sound may be obtained, due either to proximity of a pulmonary cavity to the chest wall or communication of a large open fistula with the pleural cavity. Inconstant changes in the percussion note with the mouth open or closed, on assuming the erect or recumbent posture, during inspiration or expiration, and before or after aspiration may also be noted.

A small amount of pleural fluid complicating pneumothorax and concealed in the hollow of the diaphragm may not be demonstrable by percussion although readily detected by succussion. Dulness or

flatness is generally present over large effusions but the amount is frequently underestimated, and Skoda's suggestion, *i. e.*, to estimate the amount of fluid in pneumothorax, double that indicated by percussion, if followed, will prevent some mistakes. The upper level of fluid is not always easy of determination and is likely to be placed too low, so that an instrument introduced for the removal of air may be found to be below the level of fluid. Marked mobility of the dulness over fluid and the constant maintenance of a horizontal upper border, in whatever position the patient is placed, are important and characteristic features of pneumohydrothorax, in striking contrast to the relative immobility and curved upper limit of dulness in pleural effusions without air. In two of Emerson's cases with a large amount of fluid a small amount of air could constantly be demonstrated in the uppermost point of the chest, with the patient in different positions.

Auscultation.—Suppressed or absent breathing combined with hyper-resonance on percussion is usually the first indication in the course of the examination that pneumothorax exists, and this diminution in the respiratory murmur is the more striking in contrast to the exaggerated breath sounds over the uninvolved lung. Diminished bronchial breathing may also be heard. The voice sounds and the whisper are diminished or absent. Among 90 of James' cases in which the character of the respiratory murmur was noted it was found to be diminished in 41, amphoric in 31, absent in 12 and bronchial in 6 cases.

Amphoric Phenomena.—The breathing not infrequently presents a peculiar metallic quality resembling the sound produced by blowing over the mouth of an empty decanter and hence spoken of as amphoric. This was first described by Laennec as "*bourdonnement amphorique*," and ascribed to the motion of air in and out of the pleural cavity through an open fistula. In support of this explanation it may be said that an open fistula exists in most of the cases in which amphoric breathing is heard and the point of maximum intensity of the amphoric breathing over the chest is occasionally observed to coincide with the position of the fistula found at autopsy. The factors leading to the production of this sound have been the subject of much controversy and cannot yet be regarded as settled. The report of cases by Maréchal,¹ West,² and Emerson³ in which amphoric respiration was present yet the fistula was certainly or probably closed, Powell's⁴ observation of amphoric respiration over a distended stomach and Hoover's⁵ finding of amphoric respiration over a loop of distended intestine in the left hypochondrium suggest that a communication with the pleural cavity is unnecessary. The most probable explanation seems to be that the sound is due to the resonating properties of the pneumothorax cavity and is produced by the vibration of air within the cavity itself or by vibrations propagated from neighboring parts of the lung or bronchial tree. The presence of

¹ *Jour. hebdom. de méd.*, Paris, 1829, ii.

² *Trans. Clin. Soc.*, London, 1884, xvii.

³ *Johns Hopkins Hospital Reports*, 1903, ii.

⁴ *Lancet*, March 4, 1882.

⁵ *Cleveland Jour. of Med.*, February, 1898.

fluid is unnecessary for its production. It is variable in its location, intensity, and pitch. Not only the respiratory murmur, but also in occasional instances the percussion note, cough, vocal resonance, whisper, the heart sounds, rales, pleural friction and deglutition sounds may have a metallic and amphoric quality.

Metallic Tinkle.—This is impressive and characteristic and described by Laennec as resembling the sound produced by gently striking with a pin or dropping sand into a glass, metal, or porcelain vessel; or like the vibration of a metallic cord touched by the finger. Several explanations of this curious phenomenon have been offered. Agitation of the fluid against the walls of the pleural cavity, the bursting at the surface of fluid of bubbles of air which enter through a submerged fistula, the falling of drops from the walls of the cavity above to the surface of the fluid below or the modification by a suitable resonance chamber, such as the pneumothorax cavity, of rales produced in its vicinity have been suggested. The finding of metallic tinkling in cases in which from the absence of the succussion splash there was reason to believe that fluid was absent, as in those reported by Finney¹ and Maillart and Laserre,² lends support to the last mentioned view, but as small amounts of fluid may fail to give this sign this explanation cannot be accepted without more conclusive evidence of the absence of fluid. The failure of Forbes³ to find on dissection any communication between the bronchi and the pleural fluid in a case in which metallic tinkle was most distinct suggests that the open fistula is unnecessary. The sound may be heard during respiration, speaking or coughing or after change of position. In some instances a cough may be needed to produce it and in doubtful cases this should be tried. At times metallic tinkling is audible to the patient and in Allbutt's⁴ remarkable case it could be heard for two hours in all parts of a large room. In James' series it was present in 30, absent in 5 of 35 cases in which it was mentioned. Amphoric breathing may or may not be present with it. The sign is not distinctive of pneumothorax but may be heard also over large pulmonary cavities. Hérard⁵ heard metallic tinkling over a dilated kidney containing pus and gas. The ureter was patent.

Unverricht⁶ described a peculiar phenomenon heard after withdrawal of part of the air in pyopneumothorax. With each inspiration there were sounds like those heard on smoking a Turkish water pipe ("Wasserpfeifengeräusch") and ascribed to the bursting at the surface of the fluid of bubbles entering through an open pulmonary fistula. Riegel (quoted from Unverricht) heard a similar sound, unassociated with aspiration and only when the patient assumed such a position that the fistula opened under the fluid.

Succussion Sound.—In the works formerly ascribed to Hippocrates it is recommended: "Seat him on a seat which will not stir. Let some-

¹ *Dublin Jour. of Med. Sci.*, April, 1898.

² *Rev. méd. de la Suisse Rom.*, November 20, 1902.

³ *Translation of Laennec's de l'Auscultation Méd.*, 1834.

⁴ See Finlay, *Pneumothorax*, *Allbutt's System of Med.*, 1899, vi, 378.

⁵ *Bull. de la Soc. Anat.*, 1850, vol. xxv, 98.

⁶ *Deut. Klinik*, 1903-07, p. 208.

one hold him by the arms while you shake him by the shoulders and listen to hear on which side the sound is produced." The sound resembles that produced by shaking a flask half full of water and like other sounds heard in the chest in the presence of pneumothorax may have a metallic or amphoric quality. It is the earliest and most important indication of the presence of fluid and gas in the pleural cavity and may be obtained long before fluid can be demonstrated by other means. Small amounts of fluid may fail to give the splash. Its intensity is variable. It may be heard only by the most attentive auscultation, be readily audible to the examiner and even to the patient, or in some instances appreciated in all parts of a large amphitheatre, as in James' case of left pyopneumothorax (Plate XX). At times it may be heard only with the patient erect or again only in the recumbent position. In 54 of James' cases in which it was mentioned it was present in 41, absent in 13 cases. Similar splashing sounds may be obtained from the stomach, the intestine or the peritoneum if fluid and air are present, but the site of maximum intensity and other clinical evidence will usually serve to exclude errors from these sources. In some instances it may be necessary to be sure that the stomach is empty when the test is made. The churning "mill-wheel" murmur of pneumohydropericardium can hardly be a cause of confusion. Some difficulty is occasionally experienced in differentiating pneumohydrothorax from a pulmonary cavity containing air and fluid.

Coin Sound. This is known also as the bell sound and Bruit d'Arain. It was first described in an anonymous article,¹ which attributes its discovery to Trousseau. The test is usually made by having an assistant place on the front or back of the chest a coin against which another coin is struck, while the examiner listens with the ear or the stethoscope at a point on the chest wall directly opposite. If present a clear, musical, bell-like tone is produced, resembling in its quality the amphoric phenomena previously described and quite different from the sound obtained for comparison over the unaffected side. Among 25 of Emerson's cases in which it was mentioned it was present in 20, absent in 3, suggestive in 2. In 37 of James' series, it was present in 25, absent in 12. This sound, like amphoric breathing, is probably due to the peculiar resonating qualities of the pneumothorax cavity. It is not absolutely distinctive of pneumothorax. Osler² reported its presence over a large cavity in the right upper lobe.

Gas Analysis.—In his experiments on dogs, Emerson found that if air be introduced into the chest there is an almost immediate accumulation of CO₂ and diminution of O in the pleura, but the N remains remarkably constant until a point is reached at which one may suppose that absorption is well under way, when the N rises about 8 per cent. and then remains quite constant. The composition depends on the gases of the blood and on the local respiration of the tissues. Ewald³ determined in man that the percentage of CO₂ is greater in the presence of an inflamed

¹ Pneumothorax, Nouveau signe pathognomique de cette affection, *Gaz. des Hôp.*, April 4, 1857.

² *Montreal Med. Jour.*, 1895, xxiv, 969.

³ *Arch. f. Anat. u. Physiol.*, 1876, p. 422.

pleura and greatest when there is pus. Analysis of the gas is of little assistance in judging the condition of the fistula, but an increasing amount of oxygen in portions of gas successively removed suggests an open fistula as in Leconte and Demarquay's¹ case.

Air or gas which has gained entrance to the pleural cavity is absorbed, the rate of absorption varying with the condition of the pleura and the composition of the gas. Absorption is most rapid when the pleura is normal. According to Szupak's² investigations on dogs, atmospheric air, O and CO₂ are absorbed at about the same rate, while N is taken up only about one-half as rapidly. In his review of clinical cases he finds that the time required for absorption in cases without friction rub or fluid exudate was from twenty-six days to two months. In one case the air was absorbed in six days and in another after three years. The possibility of slow leakage of air through the fistula and inhibition from inflammation of the pleura must be considered and are probably largely responsible for wide differences in the apparent rate of absorption.

X-ray Examination.—This not only serves to confirm the results of physical examination but may show small collections of air not otherwise to be detected. Both the fluoroscope and the radiograph should be used. Examination in the erect posture is usually most satisfactory. The position of the displaced heart, fractures of the ribs, and depression of the diaphragm may be noted. An accumulation of air is seen as an abnormally clear zone, over which the normal lung markings are absent and the ribs more sharply defined than at other parts of the chest. For the detection of small bubbles of air above pleural effusions Kraus recommends examination with the body inclined at an angle of about 45 degrees and finds that air can thus be detected when nothing is seen in the erect position. The collapsed lung is seen as a relatively dense, sharply limited, irregularly oval shadow in the mid-chest in the region of the root of the lung. An incompletely retracted normal lung is less dense. Infiltration of the tissue may be responsible for failure to retract and may add to the density of the shadow. Adhesions may account for irregularities in the contour of the lung and appear as linear or band-like connections between the lung and the chest wall. Inspection of the other lung may disclose suggestive evidence of tuberculosis.

The presence of pleural fluid adds much that is interesting, instructive, and distinctive to the picture. It appears as an opaque shadow at the bottom of the chest and, what is most significant, with its upper border constantly horizontal, independent of the patient's position. With the patient upright the upper border is transverse. When he lies on his side it is parallel to the long axis of the body. The upper border is most sharply defined when the tube is in line with the level of the surface of fluid. Examination with the fluoroscope shows a wavy motion of the surface on shaking the patient, tapping the abdomen with the fingers, percussion of the chest, or during cough. Careful inspection when the patient is still discloses also a depression of the level of the fluid during expiration and elevation during inspiration, a paradoxical phenomenon

¹ *Gaz. méd. de Paris*, 1863, vol. xviii, third section 1, 114.

² *Experimentelle Untersuchungen über den Pneumothorax*, Dorpat, 1891.

probably due to lack of diaphragmatic tone on the affected side in consequence of which respiratory changes in abdominal pressure are transmitted to the fluid. Inspiratory elevation and expiratory depression from contraction of a diaphragm which is inverted and convex below seems a less likely explanation. Still another motion is synchronous with cardiac systole, coincident with which very small waves start from the mediastinal region and travel across the surface to the chest wall.

Varieties.—Open Pneumothorax.—In this the mechanical relations are simple. An open fistula connects the pleura with the outside air and atmospheric pressure exists in the pleural space with respiratory oscillations about the zero-point. If the fistula is wide open the collapsed lung takes little or no part in respiration and the intrapleural pressure remains nearly constant at zero. If the fistula is small the respiratory oscillations are greater and the pressure may become negative in inspiration and positive in expiration. In order to maintain its patency the fistula in the collapsed lung must usually be large, with rigid walls, and run in a direction perpendicular to the pulmonary surface; hence it is uncommon as a result of perforation of the lung, but occurs more often in advanced pulmonary tuberculosis, occasionally in empyema rupturing through the bronchi and may follow thoracotomy.

Respiratory embarrassment is due to collapse of the lung and displacement downward of the diaphragm and of the mediastinum toward the sound side. Mediastinal displacement limits the excursion of the sound lung and the efficiency of respiration. Instability of the mediastinum aggravates the symptoms. If free to move, it is drawn toward the sound side during inspiration and moves toward the affected lung during expiration, in consequence of which a part of the expired air may be forced into the collapsed lung. During inspiration air is drawn not only from without into the trachea but also from the collapsed lung. The oscillation from one lung to the other of a volume of used air, the so-called "pendulum-air" of Brauer, still further reduces the efficiency of respiration. During forced expiration with cough, inflation of the collapsed lung is increased.

Valvular Pneumothorax. This is the commonest form and is due to valve-like action of the fistula, which permits entrance of air into the pleura, but prevents its escape. Rupture of a small pulmonary cavity may connect the bronchi and pleura by way of a long, narrow, sinuous passage. Inspiration inflates the partially collapsed lung and draws air into the pleural cavity, but with the collapse of the lung during expiration the fistula is closed by apposition of its walls and the imprisoned air cannot escape. The deeper the inspiration the more air enters. Cough with closed glottis greatly increases intrapulmonary pressure, inflates the collapsed lung, opens the fistula, and further distends the pleura. Tuberculosis is the cause in a large proportion of such cases.

The high degree of pressure which may be produced makes this form especially dangerous and encroachment on thoracic space and dislocation of the mediastinum may become extreme, with displacement of the heart, kinking of the great vessels, narrowing of the principal bronchi and diminished volume, elasticity, and effectiveness of the sound lung.

Mobility of the mediastinum increases the danger and thus the condition is more serious in young and healthy persons. The outcome depends on the behavior of the fistula. Total collapse of the lung favors healing of the fistula, but at times after partial absorption of air and reinflation of the lung the fistula again opens.

Pneumothorax Acutissimus.—This is also known as suffocative pneumothorax and the term is applied to cases in which death results within a few hours. A valvular fistula with the rapid development of a high positive pressure or grave complications in the lung or other organs may be responsible.

Closed Pneumothorax.—This is only a phase of the open or the valvular form and is favorable, since closure of the fistula is the necessary forerunner of recovery. The orifice of the fistula may be sealed by pleural inflammation or adhesion and union of the walls of the fistula. Collapse of the lung favors closure of the fistula and small perforating wounds or slight pulmonary lesions in a comparatively healthy lung may readily close in this way. This form is common in spontaneous pneumothorax, in relatively early tuberculous cases and after thoracentesis.

Double Pneumothorax.—This is uncommon. When it occurs death usually follows within a few hours. Life can be maintained only when the collapse of one or both lungs is incomplete. Hellin¹ has collected a number of cases.

Partial Pneumothorax.—In this form adhesions limit the air to a circumscribed area. Any portion of the pleural space may be the site. An apical localization may readily lead to confusion with a pulmonary cavity. Monnier's² case in which the position of the pneumothorax in the interlobar septum was proved by autopsy is of special interest because of its rarity.

Artificial Pneumothorax.—In 1882 Forlanini³ suggested the possibility of treating pulmonary tuberculosis by establishing artificial pneumothorax on the affected side, and in 1894 reported that he has used the method and described his technique. In 1898 Murphy⁴ reported 5 cases thus treated. The method attracted little attention and received no encouraging support until within the last few years, during which a rapidly increasing number of publications has appeared. Forlanini⁵ has recently considered the method at length and reviewed the literature.

Theories.—The method is based on the assumption that, as for tuberculous processes elsewhere, immobilization is favorable for the arrest of a tuberculous process in the lung and may be secured by the insufflation of pure nitrogen into the pleural sac on the diseased side, this gas being used because of the slowness with which it is absorbed. Compression of the lung is also regarded as an important factor, by diminishing the size, evacuating the contents and approximating the walls of pulmonary

¹ *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, xvii.

² *Gaz. méd. de Nantes*, November 2, 1907.

³ *Gaz. d. osp.*, 1882, iii; *Gaz. med. di Torino*, 1894, lxv.

⁴ *Jour. Amer. Med. Assoc.*, 1898, xxxi.

⁵ *Ergebnisse der inneren Med. u. d. Kinderheilk.*, 1912, ix, p. 621.

cavities, lessening the amount of infectious material and thus retarding the activity of the tuberculous process. Changes in the lymph circulation following the compression are supposed to diminish the absorption of toxic material and favor the development of connective tissue.

Concerning the effects of the immobilization and compression of one lung upon the other, which must of necessity work harder, it is further assumed that the tuberculous lesions, almost invariably present although of less extent, are favorably affected by an increase in respiration, blood and lymph circulation, and improvement in nutrition.

Indications.—This method is regarded as indicated in cases of pulmonary tuberculosis, after unsuccessful trial of other well-known methods, and in unilateral cases with freedom of the pleura from adhesions. Some would include the predominantly unilateral cases with slight and relatively inactive processes in the opposite lung. The treatment is also recommended for intractable hemothysis when its source from one or the other lung can be determined with tolerable certainty. Selected cases of bronchiectasis and pulmonary abscess or gangrene are also considered suitable. Obliteration of the pleural sac, acute bilateral processes and grave cardiac or renal lesions are looked upon as contraindications. An x-ray examination is a necessary preliminary in the selection of cases.

Apparatus.—The apparatus used by Forlanini¹ or its modifications by different workers² consists of two glass receptacles connected by glass or rubber tubing. Out of one receptacle nitrogen can be forced into the pleural sac by water or air pressure in the other, the water meanwhile acting as a seal to prevent the escape of nitrogen in other than the right direction. A manometer is so arranged that it can be brought into or out of connection with the nitrogen system and the pleura. A special needle is used for the puncture. The nitrogen should be chemically pure and filtered through cotton on its way to the chest.

Methods.—In choosing the site for the injection, freedom from pleural adhesions is the most important determining factor and the injection is made wherever the pleura seems most likely to be free, although the lower parts of the chest least covered with muscular tissue are regarded as points of election. Freedom of the pleura from such a degree of adhesions as would be likely to prevent the production of pneumothorax is suggested by mobility of the pulmonary margin over a part or the whole of its extent as determined by x-ray examination, percussion of the complementary space during forced inspiration and expiration and observation of the diaphragm shadow. Diminution in amplitude or total absence of respiratory motion suggest partial or complete obliteration of the pleura, but may also be due to such other causes as immobility of the lung from disease, weakness of the respiratory muscles, and increased intra-abdominal pressure. A history of pleurisy on the affected

¹ Apparate und Operationstechnik für den künstlichen Pneumothorax, *Deut. med. Wochens.*, December 14 and 21, 1911. For detailed descriptions of the apparatus the reader is referred to the article quoted.

² Robinson and Floyd, *Arch. Int. Med.*, 1912, ix, 452; Balboni, *Med. Comm. of the Mass. Med. Soc.*, 1912, xxiii.

side, lobar pneumonia as a cause of the process or pleural pain during the development of the disease may suggest pleural adhesions.

In the performance of the injection, two methods are in use: in the Murphy-Brauer method, preceding the first injection an incision is made to the parietal pleura through which the needle is obliquely introduced; in that of Forlanini, thoracentesis is performed without preliminary incision. The incision method diminishes the danger of puncture of the lung and gas embolism, but is likely to result in a greater or less degree of subcutaneous emphysema. After the first injection it is customary to give subsequent treatments by the puncture method.

Preceding the puncture the skin should be frozen with ethyl chloride. The skin and underlying tissues are then thoroughly anesthetized with 1 per cent. novocain, containing 1 to 10,000 adrenalin (Robinson). The needle, unconnected with the apparatus and with the stop-cock on the lateral outlet closed, is introduced to what seems a proper depth, the trocar is removed, and the needle-cock closed. The needle is now connected with the manometer of the apparatus, the nitrogen system meanwhile remaining closed. The position of the point of the needle just within the two layers of the pleura is indicated by the appearance of *negative pressure and marked respiratory oscillations* in the manometer, in the absence of which it is never safe to proceed with the injection which must be abandoned or another site chosen. If the point of the needle is in the thoracic wall, in a bloodvessel or in an adherent pleura, negative pressure and respiratory oscillations are absent; if in the lung, respiratory oscillations may be present, but there will be no constant negative pressure. If the point of the needle lies in the endothoracic fascia, *slight* negative pressure and respiratory oscillations may be present. Aspiration by means of a syringe attached to the needle may help to exclude the possibility of puncture of a vein.

If the desired negative pressure and respiratory oscillations are obtained, the manometer is excluded and the nitrogen system brought into connection with the needle, through which nitrogen is allowed to flow into the pleural sac under very slight pressure, to an amount varying usually from 50 to 500 cc. Small amounts are reinjected at intervals commonly at first each week. The amount and frequency are determined by the conditions in individual cases, the indication being to maintain the affected lung completely immobile. Distress or pain during the injection indicates a dangerous degree of tension on adhesions and makes it wise to terminate the procedure. The length of time over which the treatment is to be carried out cannot be definitely stated and will depend on the result obtained. It has been maintained for as long as ten years in one of Forlanini's cases.

In cases in which there is reason to believe there may be pleural adhesions at the site of the puncture, Forlanini is not deterred, but believes that the procedure can be accomplished by a modified technique. The adherent pleural space cannot be detected in the manner already described and the nitrogen must be introduced under pressure to forcibly separate the adhesions. With the needle in place, minimal amounts of nitrogen are injected by pressure upon the rubber tubing. By pressure

with the thumb and forefinger of the right hand the tube is closed at a point about 3 cm. from the connection with the needle. Compression of the short section of tubing thus isolated with two fingers and the thumb of the left hand expresses from the point of the needle about one-half cubic centimeter of nitrogen. If pressure on the tubing is now released and the tension tested the behavior of the manometer will disclose the presence of the expressed nitrogen in a closed vesicle within the tissue, its more diffuse distribution between the layers of the pleura or entrance into a vessel.¹

Dangers.—Embolism is the most immediate danger and when it occurs is commonly fatal if large amounts of gas have entered a vein. Of 98 cases treated by Forlanini this accident occurred with a fatal result in two during a repetition of the injection. Three fatal cases by the puncture method were reported to Brauer² by other operators and one occurred in his own experience. Many isolated examples are reported in the literature. Hemiplegia has followed. Sudden death apparently due to irritation of the pleura ("eclampsic pleurisy") is occasionally observed, but may follow puncture of the pleura for any reason. Thorough local anesthesia previous to the injection will probably largely prevent it. Infection may follow the introduction of organisms from within or without. Fagioli³ noted the development of pleurisy with effusion in 10 to 23 cases in which he had produced artificial pneumothorax. In other series, pleurisy is often noted in a small proportion of the cases. Emphysema of greater or less extent is common after the Murphy-Brauer incision method, but is more annoying than dangerous. It was observed in 60 per cent. of Robinson and Floyd's cases. It is less frequent when Forlanini's puncture method is used. The rapid evacuation of the contents of tuberculous cavities under compression may lead to further infection in near-by or remote parts of the lung. Dyspnoea and collapse from displacement of the mediastinum and heart, pain from the stretching of adhesions, and gastric symptoms from displacement downward of the diaphragm may follow.

It is difficult to understand how if immobilization of one lung is of value in checking a tuberculous process, overwork is good for the other, and the arguments in its favor seem invalid.

Results.—Among the more immediate effects are diminution of fever and disappearance of night-sweats. This is ascribed to diminished absorption of toxic material. The amount of sputum may at first increase, with later diminution in the cough and amount of expectoration. In a few instances, apparent arrest of the tuberculous process has been

¹ On releasing the pressure the nitrogen ordinarily fails to re-enter the tubing and the proximal branch of the manometer indicates a corresponding elevation. Immobility of the manometer even with forced breathing suggests that the nitrogen has diffused itself into the tissues or penetrated a vessel, while respiratory oscillations suggest its presence in a closed vesicle or between the layers of the pleuræ. The degree of negative pressure and the amplitude of the respiratory oscillations permit of a decision between its entrance into a closed vesicle and the pleural sac. If the latter is the case, the negative pressure and the oscillations are much more marked.

² *Verhandlungen des Congresses f. innere Med.*, 1908, 25.

³ *Münch. med. Woch.*, May 7, 1912.

secured, but detailed statements concerning the late results in any large series are not yet published.

Should the method be used? Artificial pneumothorax as a means of treatment for pulmonary tuberculosis is not theoretically sound. Bilateral infection with tubercle bacilli is almost constant and immobilization of one lung must of necessity impose a greater amount of work on the other. The dangers are considerable and sufficient to discourage support of the method, unless results so favorable as to justify the risks can be demonstrated. The results thus far are not highly promising.

Diagnosis.—When in the course of chronic pulmonary tuberculosis there is sudden pain in the side, immediately followed by severe dyspnœa, pneumothorax should be suspected. *Resonance on percussion with suppression or absence of the respiratory murmur* often gives the first intimation of the nature of the trouble. The determination of displacement of the heart away from the affected side is confirmatory and the diagnosis may be regarded as established if the succussion splash of pleural fluid is heard. Other signs of importance are diminished or absent tactile fremitus, voice sounds and whisper, the amphoric phenomena (amphoric breathing, rales, cough, vocal resonance, whisper, and heart sounds), metallic tinkle, coin-sound, and movable dulness at the base with horizontal upper border irrespective of the position of the patient. The auscultatory phenomena are essential for the diagnosis. With mild symptoms and a small pneumothorax, especially if uncomplicated by fluid, the diagnosis is difficult and the condition is probably frequently overlooked. Examination by means of the x-ray furnishes valuable data and may make a diagnosis possible when other means fail.

There may be difficulty in differentiating pneumothorax from the following conditions:

A *large pulmonary cavity*, in common with pneumothorax, may show resonance or tympany on percussion, cracked-pot sound, changes in the percussion note with the mouth open or closed, on changing the position of the patient and during inspiration or expiration. If the cavity is large and contains thin fluid, there may be movable dulness with horizontal upper border below the resonant area. Amphoric breathing, metallic tinkle, the coin sound and succussion splash may also be present. With cavity, however, the symptoms are likely to be gradually progressive, without the history of sudden pain and severe dyspnœa, as is so frequently the case with pneumothorax. With cavity also the affected side is likely to be retracted and the intercostal spaces narrowed. The upper lobes or the apex are likely to be affected over a less extensive and more definitely circumscribed area over which there is loud bronchial breathing, increase of voice, whisper and tactile fremitus and abundant rales. The heart is drawn toward the affected side and the diaphragm elevated rather than depressed. In cases where there is a large loss of pulmonary substance involving the greater part or the whole of one lung the differentiation may be difficult. Examination by means of the x-ray may be of assistance. The absence of the shadow of the retracted lung at the root and the presence of a shadow with a central clear area are suggestive of cavity.

Subphrenic pyopneumothorax, first accurately described by Leyden,¹ may offer great difficulty. A collection of air and pus is present between the diaphragm and the liver or between the diaphragm and the spleen, stomach, and colon. Perforation of a gastric or duodenal ulcer or the appendix are the usual causes, but in rare instances, as in the case reported by Umber,² gas may be formed by the colon bacillus and without evidence of perforation of the intestine. The right or left side may be affected and the diaphragm elevated as far as the third or even the second rib with displacement downward of the liver and other abdominal organs. Over the cavity containing air and fluid, occupying the lower part of the chest, there are the physical signs of pyopneumothorax. There may be resonance or tympany on percussion above, movable dulness below, diminished and amphoric or absent respiratory murmur, vocal and tactile fremitus and whisper and metallic tinkle, coin-sound, and succussion splash. Absence of cough and expectoration and a history of preceding abdominal symptoms may suggest an abdominal origin, the heart is only slightly displaced, the intercostal spaces may show inspiratory depression, the vesicular breathing terminates abruptly where the signs of pyopneumothorax begin and respiratory mobility of the pulmonary margin may be determined. Foul pus with a fecal odor may be demonstrated by exploratory puncture and an increase in the tension during inspiration and decrease during expiration, as suggested by Pfuhl, may be determined. Examination with the *x*-ray may furnish important evidence. In cases in which the pyopneumothorax is circumscribed and the upward dislocation involves only a part of the diaphragm, an abrupt dome-like elevation of the shadow may be noted, with evidence of air above and fluid below. With larger accumulations the diaphragm may be elevated as a whole, although still maintaining its oval contour with persistence of a relatively clear space in the costophrenic sinus. If, as not infrequently happens, pleurisy with effusion complicates the process, the *x*-ray picture is obscured. On examination with the fluoroscope inspiratory depression and expiratory elevation of the diaphragm may be seen and the diaphragmatic excursion is usually greater than with pneumothorax.

Diaphragmatic hernia may closely resemble pneumohydrothorax. Lacher³ and Grosser⁴ have reviewed the reported instances which comprise for the most part autopsy cases. The diagnosis is seldom made during life and in the more chronic cases has been established in only about a dozen instances.

True diaphragmatic hernia may in rare instances be congenital (the much discussed eventratio diaphragmatica being of this sort), but is more commonly acquired as the result of stab or gunshot wounds, a fall, contusion, or concussion. The left side is usually involved and the stomach protrudes into the chest. With a large defect in the diaphragm the transverse colon, the omentum, small intestine, and even the liver

¹ *Ztschr. f. klin. Med.*, 1880, i, and *Berl. klin. Wochnschr.*, 1892, xlv.

² *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, 1900, vi.

³ *Deut. Arch. f. klin. Med.*, 1880, xxvii.

⁴ *Wien. klin. Wochnschr.*, 1899, p. 655.

or spleen may be contained in the sac. In common with pneumohydrothorax, there may be enlargement of the side, diminished respiratory excursion, diminished amplitude or absence of the diaphragm shadow, immobility of the pulmonary margin as determined by percussion, dislocation of the heart and mediastinum, tympany on percussion above with dullness shifting with change of position below, coin sound, diminished respiratory murmur, voice sounds, and tactile fremitus and succussion splash. On examination with the *x*-ray, an area suggesting air above and fluid below may be seen, and, as in pneumohydrothorax, the fluid may be seen to maintain a horizontal upper border on changing the position of the patient. Waves of surface motion may also be observed during respiration and with cardiac systole.

A history of trauma, such gastro-intestinal symptoms as pain, attacks of colic, nausea, and vomiting and, in rare instances, hematemesis and the absence of cough and expectoration may call attention to the abdomen as a source of the disturbance. Changes in the physical signs dependent on a full or empty stomach, sounds over the chest resembling the movement of flatus in the intestine and the absence of stomach tympany at its normal position after inflation with gas may serve to suggest the diagnosis. The *x*-ray examination may show inspiratory depression and expiratory elevation of the fluid (unlike the paradoxical mobility in pneumohydrothorax) and after a bismuth meal the position and outline of the stomach or intestines in the thorax.

In *pneumonia* over and beside the consolidated area and in *pleurisy with effusion* over the collapsed lung the percussion note may have a tympanitic and metallic quality and amphoric auscultatory phenomena may be present, but in the former the history and clinical course and in both the increase of voice, whisper, and tactile fremitus and the absence of metallic tinkle, coin sound and succussion splash and movable dullness with horizontal upper border usually serve to make the differentiation.

Recognition of the *type* of pneumothorax is not always easy nor is it usually of practical importance. In the valvular form the dyspnoea is likely to be severe and persistent or gradually increasing with distension of the side and marked dislocation of the heart, mediastinum, and diaphragm. Intrapleural tension is likely to be persistently positive. With open pneumothorax, the dyspnoea, distension of the side, and dislocation of organs is less marked. Changes in the percussion note with the mouth open and closed are more likely to be present. Intrapleural tension is that of the atmosphere with respiratory oscillations about the zero-point and there is a rapid return to atmospheric pressure after aspiration. A gas analysis which shows 5 per cent. or less of CO₂ or a persistent increase in O in successive portions removed suggests an open fistula. When the pneumothorax becomes closed the dyspnoea diminishes, displaced organs return, positive pressure may persist at the height of inspiration and gas analysis may show a large percentage of CO₂. The determination of the cause is important. A history of preceding hemoptysis out of a clear sky or a primary pleurisy, cough for several months, night-sweats, fever, and failing weight and strength usually indicate tuberculosis, which owing to the compression of the

lung oftentimes can be established by the finding of tubercle bacilli in the expectoration. The fact that from 80 to 90 per cent. of all cases are of tuberculous origin may well influence a decision in doubtful cases, and all cases should be regarded as tuberculous until proved otherwise.

Course and Prognosis.—This depends for the most part on the underlying disease. The pneumothorax is of itself usually of relatively little importance, as the patient soon develops a tolerance to the condition. Air alone does not irritate the pleura and is usually absorbed in the course of from one to two months.

As a complication of pulmonary tuberculosis, however, it introduces very definite dangers and hastens the fatal termination. The rupture of a small subpleural tubercle, a tuberculous cavity or a pleural adhesion usually leads to tuberculous or pyogenic infection of the pleura, with the formation of a serofibrinous or purulent effusion, in consequence of which the fever becomes more marked and emaciation progresses more rapidly. West¹ finds the mortality highest in the first few days, 10 of 39 cases dying on the first day, 18 during the first week. Among 74 cases, 45 died in the first month. The general mortality was about 70 per cent. Among Drasche's 198 cases, 71 per cent. died within the first fourteen days. Death may be ascribed to suffocation from the pneumothorax itself or flooding of the opposite lung with pus, to rapid extension of tuberculous or septic material into the pleura or to the original disease, phthisis. Hughes² remarkable patient lived at least three years and two months after the occurrence of pneumothorax, was able to attend his regular business and amused his friends by the succussion sound. In a small proportion of the cases an effusion fails to develop, or if present is absorbed or successfully evacuated and the patient's recovery is permanent and complete.

Spengler³ has reported 10 cases of tuberculous pneumothorax with recovery and in 6 there was simultaneous arrest of the pulmonary tuberculosis, but his experience has been very unusual and contrary to that of most observers. To the time of his report a total of 38 cases of healed tuberculous pneumothorax could be found in the literature. The favorable outcome in these cases has been used as an argument in favor of artificial pneumothorax in the treatment of pulmonary tuberculosis, but it must be remembered that recovered cases comprise only a small proportion of the total number. West estimates complete recovery at not over 10 per cent., and this may be regarded as a conservative estimate.

The prognosis of the spontaneous cases, unless of the suffocative type, is favorable, only one death occurring in 58 cases studied by Fussell and Riesman. Uncomplicated traumatic cases usually also do well. Suffocative pneumothorax is rapidly fatal unless relieved by operation.

Treatment.—The indications are, on the one hand, to promote closure of the pulmonary fistula and prevent infection of the pleura and on the other to relieve a dangerous degree of embarrassment to respiration and the unfavorable consequences of pleural effusion more especially

¹ *Lancet*, 1897, i, 1264.

³ *Beitr. z. klin. Chir.*, 1906, xliv, 68.

² *Guy's Hosp. Rep.*, 2d S., viii.

of the purulent form. Inasmuch as removal of air or fluid by decreasing intrapleural tension tends to reinflate the collapsed lung, reopen a pulmonary fistula, and aspirate infectious material from the lung or bronchi into the pleura, the indications are mutually conflicting and a conservative middle course is often the wisest plan.

In ordinary and other than urgent cases immediately following the rupture the patient should be absolutely at rest in bed. Irritative and unproductive cough should so far as possible be suppressed and deep respiration avoided in order to hasten closure of the fistula and prevent further entrance of air into the pleura. Strapping the affected side with adhesive plaster may help and morphia may be of assistance in quieting cough. In mild and moderately severe cases no further treatment is usually needed. The patient should be absolutely quiet for two or three weeks or until there is reason to believe that the fistula is closed. Traumatic and spontaneous cases usually do well under such treatment.

In cases in which the pneumothorax rapidly increases, with urgent dyspnoea, cyanosis and great displacement of the heart, immediate relief must be offered. Pneumothorax acutissimus and certain cases of the valvular form are of this type. Puncture may prove life-saving. Aspiration should be avoided for fear of reopening the fistula. With valvular pneumothorax the pleural sac is likely to be reinflated and the puncture may need to be repeated or the cannula left in place for a time. Infection through the chest wall is to be avoided by the strictest asepsis. Thoracotomy with insertion of a drainage tube, converting the valvular into open pneumothorax with external fistula, is occasionally necessary.

With hemopneumothorax and hydropneumothorax with a small or moderate amount of fluid and without pressure symptoms, it is best to leave the fluid undisturbed for at least two or three weeks or until closure of the fistula is established. With large fluid accumulations or those with pressure symptoms it may be necessary to tap, but it is best to withdraw only small amounts at frequent intervals and without forcible aspiration. The indications are essentially those with uncomplicated serofibrinous effusions with the exception that here the danger incident to the fluid must be weighed against that of opening the fistula and the latter justifies a delay in doubtful cases.

Spengler regards an exudate as desirable to promote closure of the fistula, further compression of the lung and arrest of the tuberculous process and would allow the patient to be up and about as soon as possible to deepen respiratory motion and induce pleural infection. Such an extension of infection to the pleura seems to the writer undesirable and to lead to more rapid progress of the disease.

With seropurulent and sterile purulent effusions in which symptoms of sepsis are absent or slight, it is best if possible to wait until the fistula is closed. If removal is indicated, simple aspiration and the repeated removal of from 500 to 700 cc. may suffice. With frankly purulent fluid containing pyogenic organisms and with marked symptoms of sepsis, further regard for the fistula must be abandoned and permanent and free drainage established as for ordinary empyema. With putrid exudates an immediate operation is demanded.

CHAPTER XXX

DISEASES OF THE MEDIASTINUM

By HENRY A. CHRISTIAN, A.M., M.D.

Introduction.—As ordinarily used, the term diseases of the mediastinum is purely a conventional one. It does not comprise all diseased conditions of the organs situated in the mediastinum, but only such as are not conveniently grouped under other headings. Under diseases of the mediastinum it is convenient to consider neoplastic and inflammatory conditions which originate in or chiefly affect the mediastinum. Almost all of the conditions to be described have their main seat in the superior mediastinum, that part above the upper border of the heart; it may be convenient at times further to divide this into an anterior and posterior part by a plane passing laterally through the trachea, but a strict anatomical subdivision will not add to the clearness of the subject. Rather it is the purpose to consider the mediastinum as a whole and to discuss the effect of diseased conditions on its contents, with only occasional reference to an anterior and a posterior, a superior and an inferior mediastinum.

TUMORS OF THE MEDIASTINUM

Of diseases of the mediastinum tumors form the group of greatest interest and importance. Both primary and secondary tumors occur in the mediastinum. Primary tumors may take their origin from any of the structures in this region, but probably their most frequent origin is in the mediastinal lymph nodes and thymus. Secondary tumors enter the mediastinum either by metastasis or by direct extension. They are usually small and of themselves clinically unimportant. If large, they produce symptoms and physical signs like those of a primary tumor.

In the mediastinum with its complex content a variety of primary tumors may develop. Fibroma, lipoma, chondroma, osteochondroma, myoma, sarcoma, carcinoma, simple cyst, dermoid cyst, and teratoma occur. All of these except sarcoma, carcinoma, and rarely teratoma, are benign, in the sense that they do not invade or metastasize. However, since the mediastinum is a confined space of small dimensions, containing many important structures, any one of these in its growth may produce serious pressure symptoms, and tumors, which in other parts of the body are of little moment, may prove fatal here, even before attaining any very great size.

Simple benign tumors, such as fibroma, lipoma, chondroma, and myoma, are of very infrequent occurrence in the mediastinum, and

often are accidental postmortem findings. Cases which, during life, have shown symptoms due to their presence, are as yet too few to justify any attempt to construct a special symptomatology. It is sufficient to bear them in mind in connection with patients showing slight long-continued signs of mediastinal tumor. If diagnosed there is a good chance of successful surgical removal.

In contrast to the simple benign tumors are those remaining for consideration (sarcoma, carcinoma, cyst, and teratoma). These are not excessively rare, but form a fairly definite though small proportion of hospital medical cases (1 to 500 at St. Bartholomew's Hospital, London). Furthermore, their clinical course and physical signs are sufficiently characteristic to lead to a correct diagnosis in the larger percentage of the cases.

Sarcoma.—This, of all tumors of the mediastinum, is of most frequent occurrence, although in the older books carcinoma is given as the most common primary tumor. This, however, is undoubtedly due to errors in terminology and diagnosis. Hare, in whose collection of 520 cases of mediastinal disease 98 are given as sarcoma and 134 as cancer, merely classifies them according to the author's diagnosis, without any criticism of its correctness, and does not exclude secondary tumors. This apparent frequency of cancer is due to the earlier use of this word for any cellular malignant tumor, shown by the fact that the larger number of Hare's cases of cancer antedate 1880, while the reverse is true of the sarcoma. The very great preponderance of sarcoma over carcinoma in the recent literature shows the comparative infrequency of the latter. At present, classifying tumors on a structural basis, we reserve the terms carcinoma and cancer for tumors clearly epithelial in structure and cell grouping. Such are undoubtedly infrequent in the mediastinum, while tumors structurally of the sarcoma group are relatively frequent.

Sarcoma can originate in the loose connective tissue, in the peribronchial and mediastinal lymph nodes, and in the thymus. It is not possible to determine which of these is the most common point of origin, since in few cases at autopsy are the relations or the structure such as to definitely reveal the beginning point of the tumor.

Structurally we may divide most sarcomas of the mediastinum in two classes, spindle-cell sarcoma and lymphosarcoma. A very few are giant-cell sarcoma or chondrosarcoma. Of these lymphosarcoma is the more common. Tumors of both kinds vary considerably in size, consistence, and color. At autopsy they are usually found to fill completely the mediastinal space and compress various of the midthoracic structures. It is unusual for mediastinal sarcomas to show any very great amount of invasive growth and they compress rather than destroy. Tumors of the spindle-cell group are apt to be of a homogeneous texture and regular contour, while the lymphosarcomas tend to be lobulate and consist of tumor masses more or less separated by bands of connective tissue.

Under the term *lymphosarcoma* we include a group of tumors of a general type, with extremes of cells and intercellular substance, as in the spindle-cell series. To them a variety of names have been given,

lymphoma, malignant lymphoma, lymphocytoma, round-cell sarcoma, lymphadenoma, etc., and the attempt has been made to distinguish different varieties, as lymphoma (benign) and lymphosarcoma (malignant). This has led to confusion, and it seems more correct and in every way preferable to group all the tumors together under one term, and for this we have selected lymphosarcoma as having the advantage of usage and fairly well expressing the nature of the tumor.

Sarcoma is not uncommon in the first decade and has been reported soon after birth. In the decades between ten and sixty the regularity of distribution is very noticeable. There seems to be no age at which sarcoma of the mediastinum is particularly common and none at which it may not occur. It is somewhat more common in males.

Symptoms.—The character of the symptoms in sarcoma of the mediastinum varies much in individual cases. However, two general types occur: (1) cases of gradual onset and progressive development of symptoms; and (2) cases with a sudden appearance of symptoms and a rapid subsequent course. The former is the more usual. Ordinarily the patients give a history of an increasing shortness of breath, particularly following moderate exertion, or there is a persistent cough. Very frequently both are present, and combined with them is a sense of fulness, with feeling of oppression in the chest, with or without moderate pain. Such symptoms gradually increase in severity, and within a few months cause the patient to consult a physician either for dyspnoea or for the discomfort or pain in the chest.

With the other group there are, as it were, no premonitory symptoms. Quite suddenly dyspnoea appears or there may be an attack of suffocation. Sometimes it is a severe cough or pain in the chest which warns the patients of impending danger. These cases may become quiescent and remain so for some length of time, but this is rarely the case, as the average duration of sarcoma in this region is less than one year.

There are many variations from these types. Symptoms are almost entirely the result of pressure; what they are depends on the structures pressed upon and the degree of the pressure. One tumor, while still small, encroaches on some important mediastinal structure with resultant early definite symptoms; another grows to considerable size before any structure is functionally involved, and symptoms appear slowly.

The most common symptom is *dyspnoea*. Rarely is this absent; ordinarily it is early and almost every patient at some time during the course is dyspnoeic. It may be the result of pressure on the heart or lungs, obstruction of the trachea or bronchi, chronic passive congestion of the lungs, or irritation or destruction of the recurrent laryngeal nerve, and these causes may act singly or in combination. In most cases it occurs in the form of recurrent attacks, at first only after physical exertion or emotion. Gradually the attacks become more and more frequent and less dependent on exciting causes. Finally, dyspnoea becomes practically continuous. Respiratory rhythm in proportion to the dyspnoea is usually slow. The dyspnoea is either inspiratory, or both inspiratory and expiratory. It may be accompanied by stridor. In the later stages the patient is prevented from assuming a recumbent posture and sleep

is more and more interfered with. In not a few cases death results from suffocation, and, in almost all, dyspnoea contributes largely to the lethal outcome.

Pain is frequent, particularly in the later stages, often severe, but in most cases not excessive. At first there is usually only a sense of weight and oppression in the chest; later, more definite pain. Not infrequently moderate paroxysms of pain occur which radiate up the neck or down the arm. There may be localized numbness or pain in one arm, the result of pressure on the brachial plexus or its roots. More rarely one sees intercostal pain due to pressure on the intercostal nerve roots near their exit from the spinal column. A number of cases have run an almost painless course and the constant, intense boring pain which characterizes many aneurysms is quite exceptional.

Patients with sarcoma of the mediastinum generally cough. This may result from vagus irritation, but more commonly is the result of bronchitis associated with pressure on the respiratory tract. In some cases cough is a dominant feature, persistent and difficult to control. Often there are paroxysms separated by varying periods of freedom. In a number of cases cough has been slight or even absent. With the cough there is practically always a mucous or mucopurulent expectoration, often very copious. Frequently the sputum is blood-streaked and in a few cases there is hemoptysis suggestive of pulmonary tuberculosis. Examination of the sputum yields no positive diagnostic evidence.

Dysphagia occurs in some cases, but is not very common as an early symptom, since the oesophagus, by its position and structure, is well guarded from obstruction due to mediastinal neoplasms.

Hoarseness and a weak voice are common later symptoms and there may be aphonia. These result from pressure on the recurrent laryngeal nerves; but it should be borne in mind that paralyzes of the vocal cords may be present without change of voice and remain undetected unless the throat is examined with the laryngoscope.

With these symptoms there is a loss of appetite, progressive muscular weakness, and a decrease of subcutaneous fat, all signs of a serious progressing malady. In sarcoma the course is, in most cases, relatively a rapid one. Death ensues usually in about six months after the development of definite symptoms and not many live longer than one year. Slowly growing, more fibrous tumors extend over a longer period, but they are not the more common form. On the other hand the course may be fulminant, as the one reported by Jaccoud,¹ with death in eight days after the first symptom.

Physical Examination.—Inspection probably yields most diagnostic information. A deformity of the upper anterior thorax, consisting of a median or mediolateral bulging of the chest wall, may be evident at a glance. In other cases no deformity of the bony wall of the thorax exists, but a slight fulness of the intercostal spaces adjacent to the sternum may be noted. Accompanying a prominence of the chest wall, or independent of deformity, a localized pulsation may be seen. This

¹ Cited by Riegel, *Arch. f. path. Anat., etc.*, 1870, xlix, 212

is much more characteristic of aneurysm, but may occur in mediastinal tumor, either as a transmitted aortic pulsation, the pulsation of a distended vein, or the pulsation of an extremely vascular tumor. The latter may be even expansile in character and closely simulate an aneurysmal pulsation; however, a systolic bruit heard over such an area is extraordinarily rare in tumor, while common in aneurysm.

In a large percentage of cases, particularly in the later stages, a dilatation of the superficial veins of the thorax and neck is apparent, and this is more apt to be unilateral than bilateral. Not infrequently the jugular veins stand out as prominent cords, or tortuous veins of considerable diameter may be seen coursing over the anterior chest. Sometimes these vessels are limited in distribution to the chest wall in front, between the clavicle and third or fourth ribs. In other cases they may extend down to or even below the level of the attachment of the diaphragm, appear in the back, and extend up along the neck or to the face. With involvement of the veins of the neck and face exophthalmos may be produced. Similarly the veins of the arm may be distended and tortuous.

Localized cyanosis is not uncommon, accompanying the venous dilatation and corresponding to the distribution of the dilated veins, although it may occur without venous dilatation. In other cases cyanosis is more general, being due to interference with normal respiration or the result of defective cardiac action. In the latter cases the cyanosis is of the nature of that common in cardiac and respiratory disease.

Rather more striking than cyanosis is localized subcutaneous œdema, with or without prominent superficial veins. The distribution of this varies in individual cases as does that of the dilated veins. Localized venous dilatation, cyanosis, and œdema result from pressure on veins, more commonly pressure on the superior vena cava or some of its larger branches. As the obstruction increases, collateral circulation takes place by way of the internal mammary, the intercostal and the azygos veins. In some cases this collateral circulation is sufficient to prevent signs of venous obstruction. The superior vena cava is rarely obstructed near enough the heart to occlude the azygos vein. In that case the collateral circulation is mainly by way of the internal mammary and superficial epigastric veins.

In a number of cases a *tumor* will be visible in the neck, either in the sternal notch or above the sternoclavicular articulation. Careful inspection of the neck may reveal deviation of the trachea from the midline or the trachea is seen to ascend a trifle obliquely from the sternal notch, both indicative of an intrathoracic mass pressing the trachea to one side.

In a few cases the position of the patient is characteristic. Some assume an attitude with the head bent forward and chin resting on the sternum. In one patient a decubitus of the forehead was produced from pressure on a table as the patient sat bent over. In other cases greatest comfort is found with the head thrown back. Some can lie only on one side. The majority of patients find most ease propped up in bed in an almost sitting posture.

Cachexia is much more common in sarcoma than in other mediastinal

tumors, but many patients maintain a surprisingly good state of nutrition. Moderate irregular fever occurs in a number.

Palpation yields additional data about thoracic deformities and pulsation. Palpation of the neck and axilla for tumor extensions or metastases is very important. Particularly is this true of the sternal notch. Here deep palpation may show a tumor mass in the upper mediastinum. Excision and microscopic study of accessible metastatic or extension nodules will yield a positive diagnosis. In all cases of suspected mediastinal mass the larynx should be palpated. In some cases it will be found fixed, no longer ascending and descending with deglutition and respiration. This is due to a mass pressing on the trachea and bronchi and fixing them. In other cases a tracheal tug, synchronous with the heart-beat, will be found. This has been reported in mediastinal tumor, but is far more common in aneurysm.

In a certain number of cases percussion reveals no evidence of any tumor mass within the chest. In an occasional case in which the tumor occupies the posterior mediastinum and produces no dulness anteriorly, percussion over the spines of the dorsal vertebræ may give an abnormal note, such as occurs in some cases of tuberculosis of the peribronchial lymph nodes, without there being any demonstrable dulness elsewhere in the back. However, in the larger number there is a localized area of dulness to be made out in the region of the manubrium sterni which gradually increases in size with the growth of the tumor. Not infrequently such an area shows not a smooth, rounded outline, but an irregular contour, suggesting a lobulated mass. Most frequently the area of dulness is small, extending a short distance on either side of the manubrium, though it may be large, involving the greater part of the anterior thorax on one side. It may be apparent also in the back. The fact that the outline of dulness, although extensive, does not correspond to the anatomical position of a lobe or lobes of the lung and does not occupy dependent portions of the thorax, in most cases serves to distinguish it from one due to pulmonary consolidation or fluid in the pleural cavity. Over the area of dulness, tactile and vocal fremitus is greatly decreased or absent. Auscultation of the dull area not infrequently is negative. In some cases, where there is dulness over the manubrium, there is an increased transmission of tracheal respiration; in others breath sounds are distant or even absent over the dull area. Auscultation outside of the area of dulness may reveal normal breath sounds, or one side of the chest may show suppressed breathing or almost total absence of respiratory sounds. On the other hand, auscultation frequently reveals numerous medium and coarse rales, often piping or sonorous in character, in one or both lungs, indicative of a more or less generalized bronchitis, resulting mainly from pressure. Laryngoscopic examination often shows paralysis of the vocal cords. The pupils may be unequal, as pressure on the nerves may produce dilatation of the pupil during the irritative stage and constriction when the nerve bundles are destroyed. In a very few cases the tumor invades the spinal column and produces pressure on the spinal cord, with consequent paralyses. Very frequently associated with the tumor there is pleurisy with effusion,

producing its ordinary symptoms. The thoracic duct is rarely obstructed, as in a case of Matzinger,¹ producing chylous ascites or hydrothorax.

Diagnosis.—The physical signs already described, taken in consideration with the symptoms, in most cases lead to the correct diagnosis. Its nature, whether malignant or benign, is shown chiefly by the course and by the extent and rapidity of development of pressure symptoms.

If there is indication of a malignant tumor, it is, in the great majority of cases, a sarcoma. Radiographic examination has been of great aid in the diagnosis of mediastinal affections. The shadow of a mass points distinctly to the diagnosis of a mediastinal affection. The absence of a pulsating outline is against, although not excluding, an aneurysm. When the contour and the shadow are irregular, there is very little probability of the mass being an aneurysm and strong likelihood that it is a tumor. Radiographs taken from time to time indicate any progressive increase in size, and when the growth is irregular the diagnosis is practically certain. Certain of the smaller tumor masses situated in the median line may escape detection, as their shadow is lost in that produced by the spinal column and the sternum. In these cases an oblique illumination may reveal what has escaped an anteroposterior one. Even without the aid of radiographs the diagnosis in most cases can be and is made antemortem. In a number of cases, however, the radiographs will give an earlier diagnosis and a clearer differentiation from aneurysm.

In very few cases is the radial pulse smaller on one side, this being much more common in aneurysm. Moreover, inequality of the radial pulses occurs in a number of other conditions, as in an anatomical anomaly of the radial artery of one side, in old hemiplegias, in sclerosis more marked in one radial, in obstruction at the mouth of the artery by sclerotic processes in the aorta, and by any form of pressure obstruction in the course of the vessel. On the other hand, high-grade signs of venous obstruction point to neoplasm.

Diagnosis from *tumors of the lung* is difficult, because these tend to invade the mediastinum early and many of the symptoms and physical signs, usually given in a consideration of tumors of the lung are due to the mediastinal portion of the tumor. After the mediastinum becomes involved, it is often impossible to tell whether the tumor was primary in the lung or in the mediastinum. A history of onset with cough and blood-stained sputum without any evidence of pulmonary tuberculosis, particularly in a person over fifty years of age, strongly suggests a primary tumor of the lung. Portions of the tumor may be expectorated and be detected in the sputum. This is unlikely in mediastinal tumor. Localized dulness of a wooden quality in the pulmonary area suggests a tumor in the lung. Vocal and tactile fremitus is decreased over this region and breath sounds are usually weak, not bronchial, in character. In some cases of tumor of the lung a change from a tympanitic to a dull percussion note during several days' observation, with a probable return to the original conditions later, occurs. This is due to a previous atelectatic portion of lung refilling with air as its bronchus becomes free

¹ *Buffalo Medical Journal*, 1901-02, xi, 755.

These signs in the absence of any evidence of considerable mediastinal growth (pressure symptoms) point to a primary tumor of the lungs rather than to a primary mediastinal tumor. Radiographic examination in some cases confirms the presence of a pulmonary mass without mediastinal involvement.

Treatment.—Little can be said with regard to this as alleviation alone is possible medically. Pain, cough, expectoration, and dyspnoea may be symptomatically controlled; cure is not to be expected. Unfortunately, at the present time, surgery has but little more to offer. The art of intrathoracic surgery, however, is developing rapidly and with the chance of the tumor being benign and possible of removal in the future surgical interference should be considered.

Endothelioma.—Only a few cases of endothelioma of the mediastinum have been reported. It is doubtful whether true endotheliomas arise from the mediastinal tissues. Those described probably have started from the pleural endothelium (mesothelium) and extended into the mediastinum. The symptoms produced in the mediastinum are those of other extensive secondary malignant growths there. With these are symptoms and physical signs due to development in the pleura.

Carcinoma.—As has been stated, primary carcinoma is not, as has been very generally although incorrectly supposed, common in the mediastinum. Aside from carcinoma arising from the œsophagus, trachea, and bronchi, the only epithelial structures serving as possible sources for carcinomas are the thymus, misplaced or accessory thyroid, and fetal remains separated in the development of the respiratory or alimentary tract. The thymus normally disappears before the age of proneness to carcinoma comes; intrathoracic thyroid more usually produces intrathoracic goitre and is considered in that connection; fetal remains are excessively rare as a source. If we eliminate cases which should be classed as sarcomas, lymphosarcomas, secondary carcinomas, pleural endotheliomas, and bronchial carcinomas, few cases remain. Josephson, working under Baumgarten, collected 46 cases of so-called mediastinal carcinoma. Only 11 of these were studied and described sufficiently well to apparently deserve the diagnosis according to Josephson and Hoffman, who think that several of these 11 are wrongly included. Löhrsch¹ has collected the cases of mediastinal tumor reported in 1896–1901 and finds but 2 of carcinoma and 2 with adenomatous parts. In 1906 Zypkin² reported a case.

A description of symptomatology based on such a small group of cases must be imperfect and is scarcely warranted. These cases, however, do show the tendency to occur in older people as would be anticipated. An invasive growth and the frequency of venous obstruction with localized œdema, cyanosis, and venous dilatation are to be regarded as points favoring the diagnosis of carcinoma rather than sarcoma and lymphosarcoma. However, before any very definite differential points can be given many more cases must be carefully studied during life and the diagnosis made certain by careful histological study after death.

¹ Lubarsch and Ostertag's *Ergebnisse d. allgemein. Path., etc.*, 1900–01, vii, 912.

² *Wien. klin. Rundschau*, 1906, xx, 34.

Simple Cyst.—Although much more infrequent than dermoid cysts, simple cysts may occur in the mediastinum. Usually these have been small and lined by ciliated epithelium. Among the accounts of 12 cysts reported, it was found that 6 were situated in close proximity to the bifurcation of the trachea, 4 near the lower end of the œsophagus, and 1 in the anterior mediastinum 4 cm. above the tracheal bifurcation. Almost all were small and in most of the cases the cyst produced no symptoms. In Fletcher's case, a girl, aged six, there was cough for one week, with dyspnoea and cyanosis for three days before death.

Bramwell's¹ case is of interest because of the difficulties in diagnosis. It occurred in a man, aged fifty, with a history of syphilis and for several years a hard drinker. He entered the hospital on account of nephritis. It was then found that he had visible, palpable pulsation over the second right interspace near the sternum, localized dullness, and a slight systolic thrill. In this region a systolic murmur could be heard and the aortic second sound was accentuated. There was no pain and no pressure symptoms. Still the diagnosis of aneurysm seemed justified. A year later he died from nephritis, and autopsy showed that the dullness was due to a cyst in the mediastinum. The pulsation was transmitted and the accentuated second sound was associated with the nephritis. The systolic murmur came from a thickening of the aortic valves.

Dermoid Cyst and Teratoma.—Among the more uncommon tumors are those which may be grouped together as dermoid cyst and teratoma. This group consists of tumors varying in complexity from a simple cyst lined by epidermis with its appendages (hair follicles, sebaceous glands, or sweat ducts) to solid tumors made up of a variety of tissues in complex arrangement. Between these two extremes all gradations of complexity are met and it is difficult so to define the terms, dermoid cyst and teratoma, that two distinct groups can be made. Furthermore, all have much in common as to origin, course of development, and symptomatology, and they can be best described together. These tumors do not occur very frequently. Hare in 1889 among 288 cases of mediastinal tumor reports only 10 dermoid cysts. At the end of 1901 the writer² was able to collect 40 such cases, and recently Morris³ has brought this number up to 57. To these are to be added 7 additional cases from the literature which increase the total to 64 cases from the first reported by Gordon in 1823 to the time of this analysis.

From the clinical standpoint it is important to keep in mind a few of the structural peculiarities of these tumors. The content of the cysts is a greasy gray to yellow semisolid material in which hair is often mingled. If this material escapes to the surface, it may be recognized and a correct diagnosis made. The tumor often includes bone, cartilage, or teeth, all of which will give a characteristic shadow on x-ray examination, and lead to a diagnosis.

The primary portion of the tumor is usually in the upper half of the thorax, wholly or in part immediately behind the manubrium sterni.

¹ *Clinical Studies*, Edinburgh, 1902-03, 145.

² *Journal of Medical Research*, 1902, vii, 54.

³ *Medical News*, September 16, 1905.

A smaller number are situated in the lower half of the thorax between the heart and the adjacent lung. In several cases the tumor extended into the neck. Development of a tumor in the upper part of the anterior mediastinum beyond a certain point would be resisted in front by the bony wall of the thorax, and behind by the great vessels and trachea supported by the vertebral column. Growth would be possible in three directions—upward through the superior aperture of the thorax, laterally into the pleural cavity, and downward between the heart and lungs—and these three directions of expansion occur in reported cases. For some tumors not situated in the upper anterior mediastinum migration from a previous position can be assumed to have taken place as the tumor increased in size.

In almost every case adhesions to some adjacent organ are found. The tumor is most frequently bound to some part of the lung and almost as often to the pericardium. Less frequently they are attached to other structures, as chest wall, diaphragm, or great vessels. These tumors, though occupying a position surrounded by vital organs and generally in actual union with them do not as a rule produce great destruction of adjacent structures. In one case the aorta was eroded, in a second there was a communication between the tumor and the pericardial cavity; in a number of cases they eroded into the lung and formed a communication with the bronchus.

These tumors are far more frequent in young adults. Of the reported cases nearly 62 per cent. came to operation between the ages of eighteen and thirty years. Sex has no apparent influence on their occurrence.

Symptoms. The onset is nearly always gradual. There is usually a latent period during which the tumor gives no evidence of its existence. Ordinarily this continues up to the time of puberty when the tumor begins to grow more or less rapidly and as it increases in size begins to press on adjacent structures and symptoms appear. This constitutes a period of activity. While this is true of most cases, in others symptoms have appeared at an earlier or later period or the tumor remained latent throughout life, to be an accidental finding at autopsy.

The onset of an active stage is by no means characteristic; indeed, it is seldom that the condition has been correctly diagnosed early. The common early symptom is dyspnoea after exertion, frequently associated with pain in the chest, at times with cough or a feeling of pressure. Less commonly pain and hemoptysis have been the initial symptoms. With progress of the growth of the tumor, dyspnoea almost always becomes prominent. In the earlier stages it is apt to be intermittent, greatly aggravated by exertion, and generally accompanied by cough with expectoration, frequently blood-tinged. In the later stages difficult breathing is more constant and severe, and may become so extreme as to cause death. Dysphagia does not occur.

Pain is frequent, although it may be slight and often is not present at all. It is usually sharp, seldom dull and aching. There is nothing typical in the cough. The expectoration, however, is of very great importance and should be carefully examined in every suspected case. The quantity varies greatly; at first it is small in amount, but later may

become very copious. The sputum may be (1) that which comes merely from the bronchi or (2) that which comes from bronchi and cyst cavity by way of a perforation into a bronchus. The first is in no way characteristic; it results from the bronchitis following pressure on the trachea or bronchi; it is the sputum of a chronic bronchitis and may occur with any mediastinal mass. The second may be characteristic and in some cases is pathognomonic. Search should be made for epithelial cells, resembling those from the horny layer of the skin, for fat droplets, fatty acid and cholesterin crystals, and for hairs. The finding of the last is absolutely diagnostic, the others highly suggestive of dermoid cyst. It is not likely that the sputum will aid in the diagnosis of a solid teratoma. In 21 of the reported cases there was a communication between the cyst and a bronchus; in 11 of these, hair was expectorated and 8 were correctly diagnosed.

Hemoptysis is quite common but is usually late. It may be severe enough to cause death. In other cases there is continued but slight loss of blood, so that the sputum is almost always blood-tinged.

The course is relatively a slow one, a period rather of years than of months. This is in strong contrast to cases of malignant disease of the same region.

Physical Signs.—The patients are usually well nourished and show no evidence of cachexia. The superficial veins of the thorax are not distended; there is no local oedema. The radial pulse is equal on the two sides. In no case has paralysis of the vocal cords been noted. Frequently the tumor produces a fulness or bulging of the chest wall, usually anteriorly. This is oftenest in the upper part of the chest from the level of the second to the sixth ribs, but may be elsewhere. This asymmetry of the chest persists for months or years, showing little or no change. The tumor may appear in the neck through the superior aperture of the thorax, and in some of these fluctuation can be made out. In others pulsation may be present, but is not expansile in character. Fistulous communication between the cyst and skin surface may form with discharge of characteristic cyst contents.

If the tumor is of moderate size, percussion almost always reveals an irregular area of flatness or dullness over which breath sounds and vocal and tactile fremitus are diminished. This is practically always the case when the tumor deforms the chest and corresponds to the prominence. The dullness is usually in front but in some cases is situated behind. Again, there may be dullness anteriorly and posteriorly with intervening resonance, or almost the entire right or left half of the thorax may be dull. Very frequently moist or dry rales are heard throughout the lung on the side of the tumor, not infrequently on both sides. When the tumor is large or situated low down, displacement of the heart occurs or the liver may be pushed downward.

Diagnosis.—When hairs are expectorated, or escape from a fistulous communication with the skin, the diagnosis offers no difficulty. Fat droplets, fatty acid, and cholesterin crystals or squamous epithelium similarly escaping from the cyst give a good clue to the diagnosis. Exploratory puncture has yielded a correct diagnosis in some cases,

having been done in several cases under the impression that pleurisy with effusion existed. The *x*-ray examination, besides showing the situation of a tumor mass, may reveal its nature, when bone or teeth form a part of the growth.

A probable diagnosis can be made when we have evidence in a young adult of a mediastinal tumor of slow progress. The duration of malignant disease is rarely as long as one year. Cachexia common in malignant disease is rare in dermoid cysts and teratomas. Pressure signs such as œdema, cyanosis, distension of superficial veins, inequality of the pupils, and laryngeal changes, are not found in connection with mediastinal tumors of this group, except in those more infrequent ones which show malignant parts. The course of the latter is like carcinoma and sarcoma, and, like them, dermoid cysts and teratomas are proved malignant when there is evidence of metastasis.

The diagnosis from aneurysm is usually not difficult. A case similar to Buchner's, where there was a communication between cyst and aorta, would of course present diagnostic difficulties, but such a condition is little to be expected and, if it occurred, the treatment would be that of aneurysm, for such it was practically. Echinococcus cysts can be differentiated from dermoids only by an examination of their contents. Other benign tumors are rare, and inflammatory processes present almost no difficulty.

Prognosis.—This, as compared with that of malignant tumors, is good, since the latter are almost invariably fatal in less than one year, but it is to be remembered that in dermoid cyst or teratoma, unless operated on, the chances for life for more than a few years are not very good.

Treatment.—Surgery presents the only hope of cure. Medical treatment other than palliative is futile and every patient should be given the chance of surgical treatment. Radical operation is rendered difficult by the proximity of vital organs, the frequency of extensive adhesions, and the danger of entering the pleural cavity with the production of a pneumothorax. Simple drainage often proves ineffectual, owing to the cyst being multilocular or to the presence of diverticula in a simple cyst. Yet modern surgery has very largely overcome these difficulties, and of 20 cases operated on, including those of early date, 70 per cent. were much benefited and a considerable number cured. Although the operation is a serious one, yet the results justify an attempt at removal in every case and offer a reasonable hope of complete cure.

MEDIASTINITIS

Inflammation is not infrequent in the mediastinum, but, on the other hand, mediastinitis is not often recognized. This is due to the fact that most often the mediastinal inflammation arises as a complication of some process elsewhere, whose symptoms mask those of the mediastinitis itself.

Inflammation in the mediastinum may be acute or chronic. In the

acute there may be simply exudation, serous, fibrinous, or purulent, into the loose areolar tissue, or tissue disintegration may take place with abscess formation. No sharp line can be drawn between the two types; whether the one or the other occurs, depends on the cause, duration, and severity of the process. For this reason in considering acute inflammation it does not seem advisable to consider separately simple mediastinitis and mediastinal abscess, but they will be discussed together as stages of mediastinal inflammation, the former mild, the latter severe, their symptoms varying chiefly in degree. In chronic mediastinitis there may be connective-tissue proliferation with mediastinal adhesions or chronic abscess, the latter almost always tuberculous in origin.

Acute Mediastinitis.—This, whether in the form of infiltrating exudation or abscess, occurs in the loose areolar and fatty tissue which surrounds the mediastinal organs. The seriousness of inflammation in this region depends on the facts that the mediastinum is a closed space structurally difficult of drainage either by nature or operative means, and that extension into vital structures is apt to take place.

Acute inflammatory processes in the mediastinum may be divided on an etiological basis into three groups—traumatic, extension, and metastatic. Of these the traumatic is the most important not on account of its frequency, but because trauma so often leads to abscess formation, rendering this group of cases most serious. Inflammation by extension is more common, but in many cases, apart from the severity of the primary disease, is of no very great importance, at least in the acute stages. Metastatic inflammation in the mediastinum is the rarest of the three.

Blows on the chest, particularly over the sternum, with or without fracture of bones, frequently cause diffuse suppuration mediastinitis or mediastinal abscess. Goodhart¹ reports an instance in which, following a blow on the chest from a log of wood, pain in the chest and great dyspnoea developed, with a fatal result in six days. Autopsy showed purulent infiltration of the mediastinum, with double pleuritis and pericarditis. A somewhat similar case (Walker²) followed a blow on the chest by a red-hot bar of metal. This patient recovered. Crushing injuries to the chest or spinal column, if not immediately fatal, sometimes produce this condition, as in an instance at the Boston City Hospital, in which, with suppuration of the tissues of the forearm about a Colles' fracture and a fracture of the twelfth dorsal vertebra, there was an abscess of the mediastinum. The tissues of the anterior mediastinum were matted together, quite firmly attached to the sternum, and infiltrated with pus, which was most abundant at the level of the third costal cartilages. The purulent fluid extended down between the pericardium and the right pleura.

Sometimes trauma appears to be the cause when there is little evidence of direct injury to the thorax. Such an example is given by Laird³ in a man who fell out of an apple tree several days before coming to the hospital. This fall gave him a thorough jarring, but did not cause any

¹ *Transactions of the London Pathological Society*, 1877, xxviii, 37.

² *Lancet*, 1884, i, 17.

³ *Albany Medical Annals*, 1904, xxv, 657.

evident local injury. Severe pain in the neck, head, and chest developed later and the region about the sternoclavicular joint became swollen, reddened, and œdematous. Incision over this evacuated about a pint of pus from the anterior mediastinum. Complete recovery followed.

Penetrating wounds of the mediastinum, with or without injury to the trachea or œsophagus, form another group in which mediastinal inflammation results. Günther reports a mediastinal abscess following a dagger wound penetrating the sternum. Traumatic injury or perforation of the œsophagus, trachea, or bronchi by a foreign body is apt to produce mediastinal inflammation. Similar results may follow instrumental perforation during operative procedures, as in passing sounds in the œsophagus, as in a case reported by Hacker. In this case the communication between the œsophagus and mediastinum was demonstrated by an ingenious test. Gauze impregnated with a 2 per cent. solution of potassium ferrocyanide was inserted in the cavity through the drainage wound, and the patient then swallowed a small amount of 2 per cent. solution of citrate of iron. The gauze was then removed and found to be blue where the two solutions came in contact, thus demonstrating the opening in the œsophagus and also indicating its location. The course of healing was followed by the same means until it was evident that the œsophageal opening had closed. This happened fourteen days after the operation.

In the group of inflammations by extension come the very numerous cases where in pneumonia the mediastinal tissues are infiltrated with serum or sero-pus. This is frequently seen at autopsy, but the mediastinitis usually gives little or no indication during life of its presence as a complication and it is rare for it to go on to abscess formation. Extension of an acute pleuritis secondary to the pneumonia is common, and any inflammatory condition of the lung, as abscess, gangrene, tuberculous cavity, etc., can so act. Cases of pneumonia with pericarditis or peritonitis frequently show mediastinitis, probably extending from the complicating lesions rather than from the primary pneumonia.

The tendency of an acute pericarditis to extend to the mediastinal tissues is well recognized and is not an uncommon postmortem finding. In some cases of general peritonitis without pericarditis or pleuritis there is an associated inflammatory infiltration of the mediastinum, probably the result of a lymphatic extension through the diaphragm.

Any ulcerative process in the trachea, bronchi, or œsophagus tends by extension or by perforation to produce mediastinitis. This is particularly true of perforation of the œsophagus owing to food particles escaping and infecting the surrounding tissues, frequently causing abscess.

Inflammation of the mediastinal lymph nodes, if the nodes soften and break down, may lead to extensive inflammation of the mediastinum. This more commonly follows tuberculosis of the lymph nodes and the abscess is apt to be chronic in nature.

Acute osteomyelitis of the sternum, ribs, or vertebrae may be the starting-point for mediastinal inflammation.

Inflammation may extend into the mediastinum from the neck. This is rare from the superficial tissues, since the downward path of the

process is well guarded by fasciæ. From the tissues about the larynx and trachea, on the other hand, extension is easier, while along the prevertebral region it is almost the rule in extensive processes, except from those in the immediate subcranial region and about the upper cervical vertebræ, where lateral extension is commoner. Inflammatory conditions of the pharynx, larynx, trachea, œsophagus, and lower cervical vertebræ are apt to extend to the deep cervical tissues and from them may descend into the mediastinum. Metastatic inflammation of the mediastinum may occur as a complication or sequel of a variety of infectious and pyæmic conditions. Cases have been reported during or following erysipelas, variola, typhoid fever, septic endocarditis, and rheumatic fever. Examples are cited by Hare and by Hoffmann.

Notwithstanding this variety of possible causes a number of cases of mediastinal inflammation have been reported whose etiology is by no means clear. As in other regions of the body, we regard them as probably infections whose portal of entry is not discovered.

Chronic Mediastinitis.—Following the diffuse infiltration of an acute mediastinitis, granulation tissue may form, resulting finally in scar tissue, binding together the mediastinal structures and interfering with their function. This is especially likely to take place with pericarditis and produce a mediastino-pericarditis. Rarely, if ever, are the digestive or respiratory tracts interfered with by such a chronic process. Occasionally the veins are obstructed and very infrequently the thoracic duct. A case illustrating the latter is given by Comey and McKibben,¹ in which from chronic tuberculosis involving the apex of the left lung the process extended to the mediastinal tissues and involved the thoracic duct in scar tissue with consequent obstruction. Chronic abscess, practically always tuberculous in origin, is an extension process from broken-down bronchial lymph nodes or carious bone. Usually abscess of the anterior mediastinum arises from the former. Tuberculosis of the sternum and anterior ends of the ribs leads to disease of the anterior mediastinum, while from dorsal Pott's disease comes abscess of the posterior mediastinum. Chronic abscess pathologically differs in most respects but little from acute abscess; clinically, except for longer duration and less marked febrile disturbance, they are similar and the symptoms of the two will be considered together.

Abscess of the mediastinum, whether acute or chronic, after remaining localized for a time, is apt to rupture either into some of the mediastinal organs or on the skin surface. Perforation into the œsophagus may occur and the pus be vomited, or into the trachea or bronchi and the pus be coughed up or inspired into the lung. Extension to the pleural cavities is common and penetration of the pericardium may take place. Rupture into the aorta (Burk²) or large mediastinal veins has been reported. In a number of cases the pus reaches the body surface along the upper border of the sternum or it may burrow for some distance in the deeper tissues and reach the surface at various points on the thorax.

¹ *Boston Medical and Surgical Journal*, 1903, cxlviii, 109.

² *Medico-Chirurgical Transactions*, 1846, xi, cited by Hoffmann.

In a woman aged thirty-five (Ballance¹), after many weeks of pain, a lump formed over the upper part and left side of the sternum from which pus was evacuated. A sinus persisted for two months, accompanied by severe pain and fever. The skin over the front of the sternum and for eight inches beyond its left border became red, cedematous, and apparently undermined. A sinus extended to the second left sternocostal articulation, where there was bare bone. Finally, the sternum was trephined, freely opened, and drained. Recovery was rapid and complete. Sometimes the mediastinal suppuration extends to the neck and the abscess may rupture in the region of the sternal notch or the sternoclavicular articulation.

Obviously in conditions with so various an etiology as mediastinal inflammations, sex or age are of no special import. As might be expected, where trauma plays an important rôle in etiology, males more often are affected, and the young rather than the old, but no very striking age preponderance is found.

Symptoms.—These vary with the extent and character of the process. Many times inflammation exists in the mediastinal tissues associated with inflammatory conditions elsewhere, without there being any symptoms pointing to the mediastinal process. In acute inflammatory conditions, thoracic pain is the most common symptom, and this is usually of a throbbing character. With this, fever, a rapid pulse, and the facies of any septic process are associated. With simple infiltration, pressure symptoms are not common, but with abscess formation, whether acute or chronic, they develop and there is a varying combination of dyspnoea, dysphagia, venous obstruction, and pressure on nerve trunks, with the train of symptoms already discussed under tumors. Pain due to nerve-root pressure may lead to errors in localizing the process, as where pain in the intercostal roots is referred to their terminals or with involvement of brachial roots is localized in the arm.

In lesser degrees of involvement, physical signs are lacking unless, as frequently happens, there is extension to the skin surface, with localized redness and induration, with or without ulceration and sinus formation. Such extension usually takes place in the upper intercostal spaces near the sternal margin. It may appear over the sternum, especially at the junction of the head and body. In the suprasternal notch or above the sternoclavicular joint is another site. More rarely penetration takes place behind in the region of the spinal column. Dulness may be elicited on percussion. With larger collections of pus, Hacker has called attention to a shifting or disappearance of this dulness with changes in the patient's position. More probably this sign will be given by cases in which, with perforation of the œsophagus or respiratory tract, there is a mixture of air and pus within the mediastinum. There may be bulging of the chest wall, fluctuation, or even pulsation synchronous with the heart-beat. In a few cases mediastinal tumor or aneurysm is closely simulated.

The course of mediastinal inflammation is usually rapid. Generally it is an acute condition developing in a few days, and extending over

¹ *Lancet*, 1888, ii, 857.

a short period only. More rarely it develops slowly over a period of weeks. The latter cases are often tuberculous in origin.

Diagnosis.—This depends largely on the combination of symptoms of mediastinal pressure with general symptoms of a septic process. Abscess of tuberculous origin presents most difficulty. Where there is extension of the process to the skin surface the diagnosis is usually easy. In connection with these cases it is well to bear in mind that in some cases of mediastinal tumor there is fever unaccounted for by any secondary inflammatory condition, although the latter may be present, as in a Boston City Hospital case of extensive lymphosarcoma of the anterior mediastinum. In this case perforation of the left primary bronchus had taken place. The tumor showed hemorrhage, and on microscopic examination there was much fibrinous and leukocytic infiltration, so that many sections appeared to be from an inflammatory rather than neoplastic process.

Treatment.—This is purely surgical. In the earlier stages poultices may aid; evacuation is called for when pus forms. For pus in the anterior mediastinum operation is relatively simple, in the posterior mediastinum access is much more difficult.

ECHINOCOCCUS CYSTS OF THE MEDIASTINUM

Echinococcus cysts occur in the mediastinum, but are very rare. Hare tabulated 8 cases; Hoffmann 4 cases. If the cysts are large enough to produce pressure, the symptom would simulate those of a tumor of slow growth.

ABDOMINAL MEDIASTINAL CONTENTS

Hernia.—A rare condition is hernia of abdominal viscera through the diaphragm into the thoracic space. Congenital defects of the diaphragm in the stillborn or in those dying soon after birth are the commonest causes. In such cases the abdominal viscera more commonly occupy the pleural than the mediastinal space. Hernia of congenital origin also occurs in the adult, but is more usually associated with some injury or strain of the diaphragm. Just behind the xiphoid cartilage the diaphragm is structurally weak. Here and behind, where there are openings in the diaphragm for the passage of vessels and the œsophagus, hernia is prone to occur, with the entrance of abdominal viscera into the anterior or posterior mediastinum, respectively. The stomach and colon are the organs more commonly concerned. These cases may be symptomless; nausea and vomiting may be associated with displacement of the viscera or there may be symptoms of pressure on the mediastinal structures. The presence of gurgling sounds in the mediastinum is the physical sign of most aid in diagnosing this condition. Death from intestinal obstruction in these cases is not uncommon. Surgical interference offers the only chance of relief.

Hemorrhage.—Slight mediastinal hemorrhages may occur in purpura, the hemorrhagic exanthemata and other severe infectious processes. Severe hemorrhages are of traumatic origin or due to the rupture of aneurisms. If the person survives the immediate injury, the blood is gradually absorbed without any harm. In some cases of considerable hemorrhage there are pressure symptoms.

Emphysema.—This is a rare mediastinal lesion. Air may enter the mediastinal tissues as the result of trauma of the thorax; tracheotomy; ulceration of the œsophagus, trachea, or bronchi; pertussis; or pulmonary disease. Usually there is a history pointing to some one of these causes. Physical examination shows partial or complete absence of cardiac dulness and in its place a tympanitic percussion note. Cardiac pulsation is neither visible nor palpable. The heart sounds are muffled. Synchronous with the heart beat there are fine crackling sounds, usually systolic in time, sometimes both systolic and diastolic. Usually there is also an accompanying emphysema of the neck, more often on the left side, and possibly of parts of the thorax. In most cases there is respiratory distress and often dysphagia.

Mediastinal emphysema is to be diagnosed from pneumothorax and pneumopericardium. In pneumothorax the heart is displaced and the cardiac impulse can usually be made out in an abnormal position. In both pneumothorax and pneumopericardium the fine crackling sounds synchronous with the heart beat are absent and there is no accompanying subcutaneous emphysema. With mediastinal emphysema the metallic tinkling sound is not present and there is no change in the position of the area of tympany with change of position. Mediastinal emphysema in itself is not serious and the air is readily absorbed. In many instances it accompanies a serious condition and may be a terminal event. The emphysema requires no treatment.

DISEASES OF MEDIASTINAL LYMPH NODES

Tumors have been considered and abscesses of lymph-node origin were discussed under mediastinitis. There remain simple hyperplasia, pigmentation, sclerosis, and tuberculosis. These will be considered in certain particulars of local import aside from general diseases of the lymph nodes and tuberculosis described elsewhere.

Simple Hyperplasia.—In a variety of conditions the mediastinal lymph nodes become moderately enlarged, due to the action of bacteria or toxic substances, and associated with lesions of the territory drained into the mediastinal lymph nodes or with general conditions affecting the lymph nodes of the body. The peribronchial group is more often affected in this way, although both the anterior and posterior mediastinal group may be. As a rule these changes produce no symptoms. Occasionally in children, with repeated or prolonged attacks of bronchitis, there is considerable enlargement of the peribronchial lymph nodes, enough to produce pressure on the bronchi and irritation of the bronchial mucous membrane. This causes cough which is often stubborn, tends

to be paroxysmal, and is apt to occur for the most part at night. The cough may resemble the whoop of pertussis, but differs in its persistence and the absence of contagion. It is rare to have any physical signs; if present they are similar to those described for tuberculosis of the mediastinal lymph nodes. Treatment, aside from measures for the primary condition, should be along the lines of general hygiene.

Pigmentation and Sclerosis.—In our civilization, carbon deposits are usually present in the peribronchial lymph nodes, and this is very marked in those whose daily occupation exposes them to an atmosphere laden with coal dust. The same conditions prevail for other occupations with similar exposure, as stone cutting and cutlery grinding. Other forms of pathological pigmentation occur, but are of very minor importance. In the great majority of persons this pigmentation produces no injury. If the condition is marked the lymph nodes are slightly enlarged and somewhat sclerosed, but this ordinarily produces no symptoms. Possibly a few cases of persistent cough may be due to the irritation of the bronchial mucous membrane by slightly enlarged lymph nodes. In some a more extensive chronic inflammation is set up with induration of the surrounding tissues and adhesions, which may lead to pressure on or perforation into mediastinal structures. Very often traction diverticula, especially those of the œsophagus, seem to be due primarily to the adhesion of sclerosed pigmented glands.

Softening and breaking down of the pigmented nodes may occur with perforation of adjacent viscera or abscess formation. A number of such cases have been reported. In most of them the bronchus, alone or with other viscus, has been perforated and putrid bronchitis and pulmonary gangrene produced. However, it is not always clear that these changes are due to the pigmentation and sclerosis alone, and it is probable that in some at least syphilis and tuberculosis have been factors. The symptoms are almost entirely the result of the adhesions with or without perforation and need no special discussion.

Tuberculosis.—Tuberculous lesions in the mediastinal lymph nodes are very common. In most cases they are associated with pulmonary tuberculosis or tuberculous caries of the vertebræ, ribs, or sternum. In a smaller number of cases the tuberculosis appears to be primary in the mediastinal lymph nodes; at least, that is the most prominent and most advanced lesion. This last form occurs especially in children.

In the mediastinal lymph nodes various tuberculous lesions occur. Of these there are three general groups—miliary tuberculosis, caseation and calcification with moderate enlargement, and proliferative lesions with tumor formation. The clinical importance of the second group is an indirect one: they form a source for tuberculous infection of other organs; by extension they produce mediastinal abscesses; they rupture into adjacent structures, bronchi, trachea, œsophagus, veins, arteries, or pericardium, with serious consequences. Apart from these the local process is practically symptomless. Occasionally the rupture of a caseous bronchial lymph node into an adjacent structure may be the cause of sudden death. The caseous mass, escaping into the respiratory tract, may obstruct the glottis and cause death by suffocation. Several

such cases have been reported. Fistulous communication with the cutaneous surface may be formed, or with this may be combined perforation of a bronchus or the œsophagus, so that air or food may be expelled from the skin sinus.

The *proliferative tuberculous lesions* of the mediastinal lymph nodes are not so frequent as the other two forms, but as a group they are of rather more clinical importance, since with them the lymph nodes form definite tumor masses which may not caseate. This form occurs in adults, but is much more common in children, in whom it forms an important group of tuberculous cases. Here we have large masses in the mediastinum, composed of enlarged lymph nodes, producing many of the pressure symptoms already described for tumors.

Symptoms.—In many cases of tuberculosis of the mediastinal lymph nodes no symptoms result. In children dying of some of the acute infectious diseases tuberculous lymph nodes are quite frequently found without there having been any symptoms during life pointing to them. When the lymph nodes are sufficiently enlarged and so situated as to produce pressure, we get a variety of symptoms. A very important one is cough due to bronchial irritation which is apt to be persistent in the form of paroxysms of spasmodic cough, often resembling pertussis. Substernal pain may occur, but more characteristic is pain in the region of the fourth dorsal vertebra. Dyspnœa may be present, as also dysphagia. Venous dilatation, œdema, cyanosis, hoarseness, and aphonia occur.

Physical examination is often negative. In some cases enlarged lymph nodes can be palpated in the suprasternal notch or fixation of the trachea during respiration may be detected. In a few cases dulness is elicited, especially behind in the region of the second to sixth dorsal vertebræ on one or both sides, near the midline or in front over the sternum. In other cases, with or without dulness near the midline behind, percussion over the spinous processes may give resonance different from that elicited under normal conditions. Koranyi has pointed out that normally over the seventh cervical spine there is flatness; from the first to fifth dorsal spines there is a gradually increasing resonance, and, from the sixth to the eleventh, resonance. In cases with enlarged bronchial lymph nodes flatness continues below the seventh cervical and modified resonance extends to a lower level than in the normal. On auscultation increased transmission of respiration and voice may be detected in these regions. Smith has called attention to a venous hum, heard over the sternum with the head thrown back, as a sign of enlarged bronchial lymph nodes. Wiederhofer attaches importance to a relatively loud expiration heard behind over the left bronchus. The x-ray examination in most cases will reveal the presence of enlarged or calcified bronchial lymph nodes.

Diagnosis.—Diagnosis in children in whom tumors are not so very common can be correctly made in many cases. In adults the difficulties are much greater, since, frequently, all the signs of tumor are closely simulated. Even confusion with aneurism may arise.

Treatment.—This does not differ from that applicable to other forms of tuberculosis unsuited for surgery.

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